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A STUDY OF EFFERENT CONNEXIONS OF THE FRONTAL LOBE IN THE HUMAN BRAIN AFTER LEUCOTOMY

BY

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PREVIOUS neuroanatomical investigations of the brains of patients who had died at various time-intervals following prefrontal leucotomy have dealt chiefly with the projection of the thalamic nuclei on to the frontal cortex. In this paper brains from patients with a short survival time have been examined by means of a silver method to trace fibres which arise in the frontal cortex to their termination in subcortical nuclei. A detailed investigation of cortico-fugal fibres undertaken by modern methods has not been reported as yet for the human brain. Meyer, Beck and McLardy (1947) include in their studies an examination of the prefronto-pontine tract and of certain long association fibres which they saw as patches of dense gliosis when degenerated. The course of these fibres, however, could only be followed for a limited distance in Nissl preparations and their terminations cannot be determined by this method. Otherwise our anatomical knowledge of the connexions of the frontal cortex with subcortical centres is derived from animal experiments, chiefly by the use of the Marchi method. The Marchi method, however, does not show the unmyelinated termination of a severed axon and can only give a very incomplete picture of the finely myelinated fibre paths which arise from the frontal cortex. Moreover, the results of different investigators have been contradictory. Recently, physiological methods have been applied to the study of connexions of the frontal lobes with the thalamus and hypothalamus by Murphy and Gellhorn (1945) and Ward and McCulloch (1947) and have led to some important findings. The information acquired, however, is still incomplete and the anatomical pathways are to a large extent still unknown.

Le Gros Clark (1948) has divided the efferent connexions of the frontal lobe into cortico-striate, cortico-thalamic, cortico-hypothalamic and descending connexions with the brain-stem. Only the connexions with the globus pallidus, the thalamus and subthalamus, the posterior hypothalamus and the mammillary body have been investigated and

the results are reported in this paper. Other connexions will be the subject of further studies which are being supplemented by cortical ablation experiments in macaque monkeys at the Department of Human Anatomy in Oxford.

Material and Methods

Ten leucotomy cases with a short survival time (7 to 20 days) were available for examination. Of these, 4 cases are described in full. The other 6 cases were examined but were excluded for a variety of reasons. In 3 the lesion was too massive and too posterior to warrant an inclusion in this series and the material was used for further confirmation of some of the results obtained. In another case the lesion was very small and entirely confined to the orbital areas and no secondary degeneration was found in the subcortical centres so far investigated. A further 2 cases had to be excluded because of fixation artefacts.

The primary lesion was evaluated by means of a series of transverse slices through the leucotomy cut and drawings were made of the macroscopic changes. In these the black areas represent complete loss of tissue and the varying degrees of shading are equivalent to the varying degree of damage to the surrounding tissue. The numerical cortical areas indicated are those of Brodmann. Where there was doubt whether the lesion involved agranular as well as granular frontal cortex Nissl preparations were made to clarify this point cytoarchitecturally. It was found that the transition area from granular to agranular cortex varies considerably in individual cases in its exact location and extent, thereby confirming Lashley and Clark's (1946) recent statement. Area 6 is marked in the diagrams only when the Nissl sections showed an entirely agranular cortex.

We have confined ourselves in this paper to the examination of three antero-posterior planes through subcortical centres which include the posterior hypothalamus and globus pallidus, the thalamus, the subthalamus, the red nucleus and the substantia nigra. The nuclei and fibre tracts which were examined are best studied in the accompanying diagrams. These represent a summary of the findings at each level and were drawn with the camera lucida. The levels vary a little for each case and, since the frozen technique was used, the size of each section is limited. Sections in other planes and at other levels were made to elucidate individual points but these are not included in the diagrams and will not be mentioned in the text. In all 4 cases the findings were essentially the same in both hemispheres so that only one side is described in full. For the demonstration of fibre and terminal degeneration Glees' ammoniacal silver method was used. In addition, closely adjacent sections were stained with cresyl violet and a myelin stain (Weil) in order to identify accurately the position of nuclei and fibre tracts. All methods were used on frozen sections. It was found that all cases did not impregnate with silver equally well and the two

cases in which interpretation of the silver picture was found to be difficult were excluded from this report. Factors which cannot be controlled in human materials, such as the long time-interval between death and fixation of the brain, may be responsible for this. The degenerative fibre changes following leucotomy were carefully compared with the normal fibre pattern of the corresponding thalamic region of two normal brains, stained by the same method and under similar conditions. One of these brains, that of a male aged 35, was fixed immediately after death and examined soon after fixation was completed. The other, that of a woman aged 72, had been in formalin for over three years and the period of delay after death before fixation had taken place is unknown. It was reassuring to find that both cases impregnated equally well with silver.

The interpretation of the silver picture is difficult. Criteria upon which the conclusions that secondary fibres and terminal degeneration following the leucotomy cut had occurred were therefore based only on gross changes of axons and terminals. Fragmentation and vacuolization together with marked swelling of fibres in their course were taken as indicative of degenerative fibre change. The difference between a normal and a degenerating fibre can clearly be seen in Plate XIII, fig. 6. The term "terminal" is used here to include both the ring-like terminal (boutons terminaux) and the free terminal or preterminal which forms the pericellular fibre plexus. The former was regarded as degenerated only when the ring form had completely disappeared and had been replaced by large homogeneous or disintegrating swellings, the latter only when broken up into fine droplets. Contrary to Carrera, Reissig and Mettler (1947), who were dealing with experimental material fixed under standard conditions, beaded fibres with no disintegration of the swelling were not regarded as degenerating. The limitations of the silver technique are fully realized. No conclusions were drawn from the presence of isolated degenerating fibres and it is possible that by applying such strict criteria connexions of minor significance have not been interpreted as such and have not been reported.

We were able to demonstrate secondary degeneration after survival times of seven, seven, fifteen and sixteen days. In a case in which death had occurred six days after the operation no evidence of fibre or terminal degeneration was found although the lesion was sufficiently large and posterior in position to presuppose considerable changes. In another case in which death had taken place twenty days after the operation, it was found that degeneration of the fine fibre or terminal was indicated by palely stained, diffuse debris. Some thick fibres were in an advanced stage of disintegration, others had already been replaced by rows of glial cells. Of the cases reported, fibre degeneration was more advanced in those with a longer survival time; not in the sense that more fibres were degenerated but that the disintegration of the individual fibre was more advanced and the typical terminal de-

generation seen in the seven-day cases had been largely superseded by drop-like degeneration of the preterminal fine fibre in the fifteen-day case. The time factor, however, may vary from case to case depending on a variety of factors such as age, treatment of the brain after death and possibly individual differences. It certainly appears to differ in different species.

Investigations

Case 1 was a young man who had been suffering from a severe paranoid type of schizophrenic illness for one year, and had not responded to electric convulsion therapy, when he underwent bilateral frontal leucotomy at the age of 24. The superior approach was employed, using local anæsthesia. After the operation he developed a persistent pyrexia and became mute and apathetic. On the twelfth post-operative day he started to vomit frequently, and on the fifteenth day he died. Autopsy some forty hours after death revealed pulmonary congestion, acute dilatation of the stomach and moderate subarachnoid hæmorrhage with medullary pressure cone formation. A leucotome entry mark was visible in each frontal lobe just dorsal to the superior frontal sulcus in Brodmann's area 9.

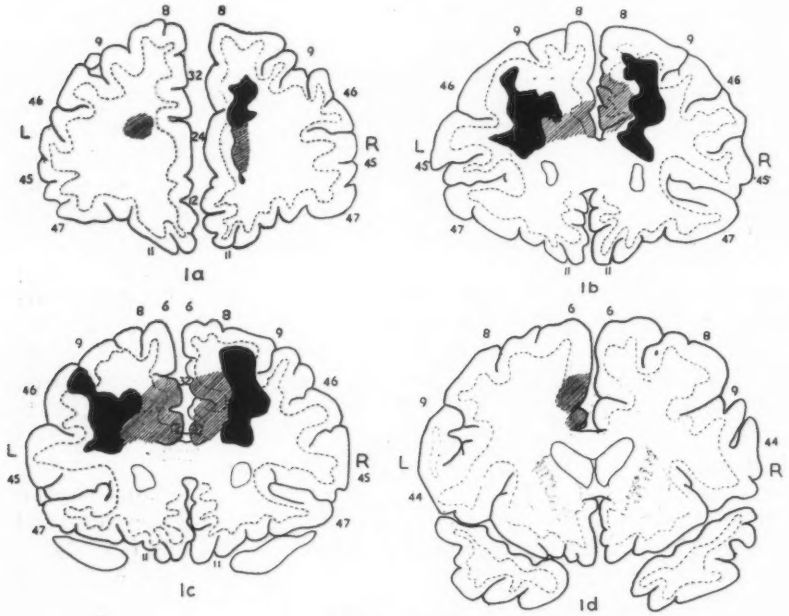

Fig. 1 (*Case* 1).

Coronal sections of the frontal lobes (fig. 1A-D) displayed a large hæmorrhagic lesion within the dorsal half of the white matter of each hemisphere. On both sides the lesion destroyed white matter deep to areas 8, 9, 46, 32 and 24 and dorsal area 45, as well as some cortex of areas 9, 32 and 24. In addition the white matter underlying the most

rostral extension of area 6 is involved on both sides. The lateral ventricles and basal ganglia were intact.

Secondary Degeneration

In this and the other text figures the distribution of axonal degeneration is shown by black lines and of terminal degeneration by coarse dots. The course of the degenerating fibres is indicated by an arrow.

Anterior level (fig. 2): Fibre fascicles in the internal capsule are cut in a longitudinal direction and, at this level, almost the entire capsule

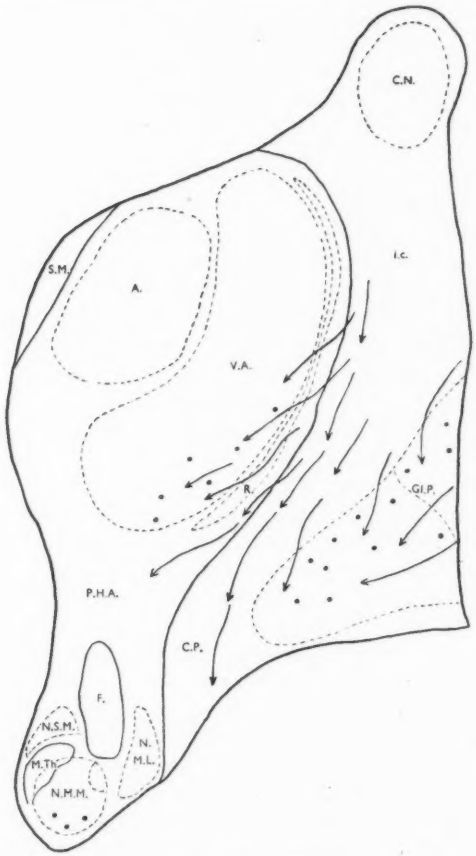

FIG. 2 (*Case* 1).

consists of fine fibres. There are few signs of secondary degeneration in the dorsal half, more in the medial level and ventrally entire fascicles are degenerated passing from here into the adjacent nuclei.

Degenerating fibre fascicles can be traced into the globus pallidus

from the internal capsule, swinging into both divisions from a dorsolateral direction. There is diffuse disintegration of much of the terminal fibre plexus (Plate XIII, fig. 8) and argentophile degenerating droplets are found surrounding a number of the large pallidal nerve cells. Degeneration of fibres and terminals is more severe in that part of the globus pallidus which is closer to the internal capsule. Apart from these fine degenerating fibres, examination at a more rostral level shows that some fibres of a larger calibre are passing into the pallidum through the putamen and some of them terminate in enormously swollen and partly disintegrated end bulbs near the external medullary lamina. Others seem to pass through into the medial division and continue to a lower level as if they were part of the internal capsule.

Across the normal fibres of the external medullary lamina and the reticular nucleus of the thalamus degenerating fibre fascicles enter the nucleus ventralis anterior. They do not penetrate deeply and are few in number dorsally, but more numerous ventrally. There is also some evidence of terminal degeneration but on the whole the changes are not very severe and much of the fibre pattern of this nucleus is entirely normal. The anterior nucleus of the thalamus is normal.

Below the level of the nucleus ventralis anterior and just dorsal to the dorsal division of the ansa lenticularis a fascicle, of which a number of fibres are degenerating, is running towards the posterior hypothalamic area. In the posterior and lateral hypothalamic areas the fibre plexus as well as the fine periventricular fibres are unaffected. It is interesting that in the lateral hypothalamic area a large number of normal boutons terminaux are observed. Of the nuclei of the mammillary body only the ventral part of the medial mammillary nucleus shows slight evidence of terminal degeneration at this rostral level. The supramammillary nucleus and the lateral nucleus are unchanged.

Middle level (fig. 3): The fibre fascicles and plexus of the anterior nucleus of the thalamus are intact, as are also the fibres lying on the floor of the lateral ventricle. The most rostral tip of the dorsomedial nucleus shows no degeneration but in the submedial nucleus there are some fine fibres in drop-like disintegration.

From the internal capsule fine fascicles of fibres, many of which are degenerated, sweep downwards and medially into the nucleus ventralis lateralis along its entire lateral margin. On reaching the medial part of the nucleus these fascicles break up into single fine fibres, presumably prior to their termination. There is much evidence of terminal degeneration which becomes more severe towards the ventral part of the nucleus. The zona incerta receives degenerating fibres from the internal capsule and single fibres also appear to cross into it from the nucleus ventralis lateralis. Some of these terminate in the zona incerta, while others proceed further into Forel's field H_2 to form part of the prerubral field of Riley. The fibre fascicles which pass through the lateral half of the subthalamic nucleus and the reticular zone of the

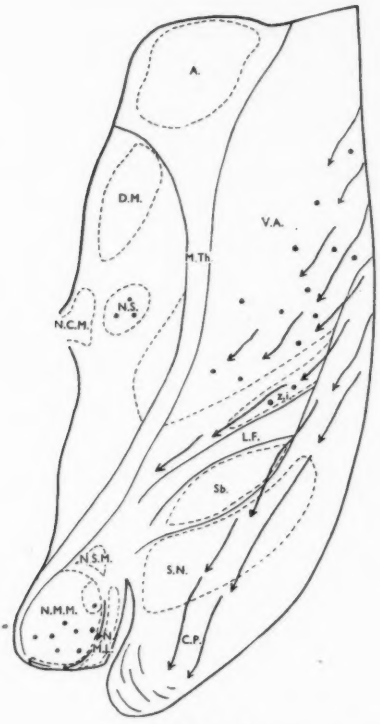

FIG. 3 (*Case* 1).

substantia nigra into the peduncle show some degeneration, but no evidence of terminal degeneration could be established in either of these nuclei. In the cerebral peduncle the fine fibres of the medial segment are entirely degenerated, in the area lateral to it about 1 in 15 fibres show typical degeneration with disintegration and irregular swelling. Fibres of the most lateral aspect of the cerebral peduncle, as seen in this section, are normal.

The medial mammillary nucleus and its lateral division show severe degeneration of the fibre plexus, particularly in the ventral part. Fine preterminal fibres have disintegrated into argentophile droplets. Enlarged degenerating end-bulbs are still visible but preterminal degeneration is more in evidence than degeneration of end-bulbs. The dorsal and dorsomedial parts of the mammillary nuclei are better preserved. The darkly stained fibres of the mammillothalamic tract, which appear to form the medial and ventral portion of the fibre capsule surrounding the mammillary body, are intact. Other fibres of the capsule, particularly at its lateral and ventral aspect, are degenerated.

In an additional section through the caudal part of the mammillary

body fine degenerating fibre fascicles are seen passing through the superior portion of the medial mammillary nucleus and degenerating end-bulbs and fine fibres in drop-like disintegration surround the nerve cells of the entire nucleus (Plate XI, fig. 2). The lateral division of the medial mammillary nucleus cannot be distinguished at this level.

Posterior level (fig. 4): The dorsomedial nucleus of the thalamus shows degenerating terminals among a large number which must be

FIG. 4 (*Case* 1).

included within the normal range. There are some fine degenerating fibres throughout. Terminal degeneration is very conspicuous in the dorsal part of the nucleus, an area ventral to the nucleus anterior which is surrounded by a lamina of intact fibres. Some fascicles of degenerating fibres enter the lateral border of the dorsomedial nucleus from the nucleus ventralis lateralis. In some areas degeneration of the terminals appears to be more severe than in others but it is impossible to

determine the limits of each with any certainty. Everywhere much of the fibre pattern has remained entirely normal.

Some degenerating terminals are seen in the area immediately ventral to the dorsomedial nucleus but it is not possible to say at this transitional level whether they are in the nucleus submedius or the nucleus parafascicularis. The arcuate, centre median and parafascicular nuclei were examined at a more posterior level in both hemispheres. There was no definite evidence that degenerating fibres terminate in these nuclei. Degenerating fibres, however, sweep through this medial region and many appear to turn ventrally in the direction of the red nucleus.

From the direction of the internal capsule a large number of degenerating fibre fascicles enter the nucleus ventralis lateralis of the thalamus. Terminal and fibre degeneration are seen throughout this nucleus, being most severe ventrally and, particularly, close to the internal capsule where there is an apparent loss of the pericellular plexus.

Degenerating fibres pass into the zona incerta via the internal capsule and also probably via the nucleus ventralis lateralis across the thalamic fasciculus. There is some evidence of terminal degeneration but the majority of the degenerating fibre fascicles pass through into Forel's field H2 where they spread out fanwise before entering the red nucleus. Any terminal degeneration in Forel's field H2 is almost impossible to identify although there is more suggestive evidence here than in H1.

Many, although not all, fibres of the fascicles which swing into the small-celled part of the red nucleus from Forel's field H2 in a dorsolateral-ventromedial direction are degenerated. Other fascicles which cross at right-angles are normal. Degenerating fascicles appear to be more frequent in the dorsolateral part of the red nucleus, where they enter; some can be followed through into the ventral part and it is possible that these terminate in the caudal division of the red nucleus or pass through to lower centres. Many of the fine fibres are degenerating, others are normal and well stained and a number of normal terminals can be recognized. Some of the fibres of the surrounding medullary capsule are degenerated. A few single degenerating fibres enter the subthalamic nucleus apparently from the internal capsule, and there is some evidence of terminal and preterminal degeneration, particularly in the lateral half of the nucleus. Its capsule is intact.

The substantia nigra is normal and contains large numbers and varieties of normal boutons terminaux. These are mainly on nerve cells and dendrites and are, in appearance, similar to those described for the anterior horn cells of the spinal cord.

The peduncle shows a few degenerating fine fibres medially and some larger ones laterally, but for the most part the fibres are normal.

The secondary degenerative changes in the left hemisphere are

fundamentally similar to those just described on the right side. The internal capsule and the ventrolateral group of the thalamic nuclei appear to contain fewer degenerating fibres than are found in the right side and degeneration in the globus pallidus is a little more severe. These variations in the severity of the degenerative process might be explained by the slight difference in the extent and position of the primary lesion.

Case 2 was a woman who had suffered from post-encephalitic Parkinsonism for 16 years before her admission to hospital at the age of 37 on account of severe behaviour disorder. Prefrontal leucotomy, using the dorsal approach, was performed under local anæsthesia a year later. She became drowsy during the operation and remained so. On the third post-operative day she developed mild pyrexia which persisted. She lay curled up in bed with her arms in spastic flexion. Lumbar puncture on the fifth and sixth post-operative days showed the cerebrospinal fluid to be blood-stained and under slightly increased pressure. She became comatose and hyperpyrexic and died on the seventh day after operation.

Autopsy, performed twenty-one hours after death, revealed no significant abnormality in the bodily organs. The convolutions of the cerebral hemispheres were flattened, most conspicuous in the right frontal region. Subarachnoid hæmorrhage was present in both Sylvian fissures and over the orbital surface of both frontal lobes. There was evidence of herniation of the cerebellar tonsils. A leucotome entry mark was visible within the superior frontal gyrus of each hemisphere in the region of Brodmann's area 8.

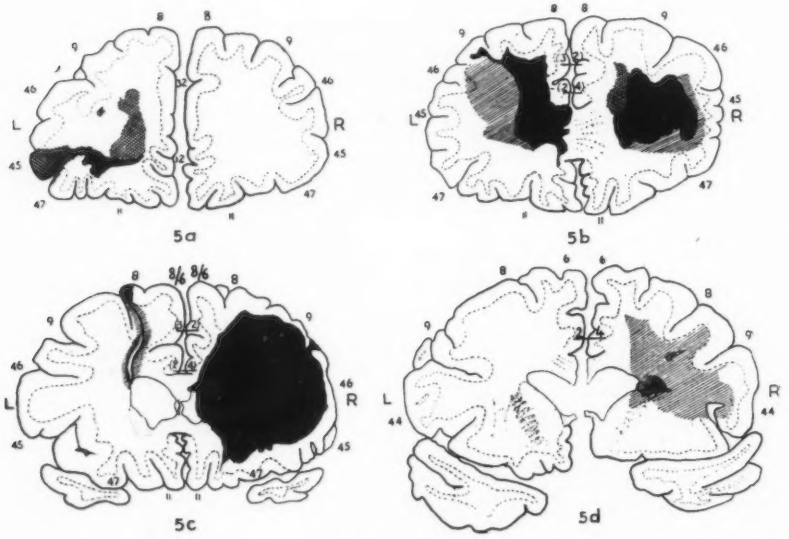

FIG. 5 (*Case* 2).

Coronal sections of the frontal lobes (fig. 5A-D) revealed on the right side a large blood clot occupying almost the entire centrum ovale involving the white matter which underlies the premotor cortex, and

also the head of the striatum. On the left side a more slit-like, ragged-edged lesion cuts most of the white matter at the level of the tip of the anterior horn of the lateral ventricle. Both lateral ventricles and the third ventricle were filled by blood clot.

Secondary Degeneration

Anterior level (fig. 6): In the internal capsule the fine and thick fibre fascicles are severely degenerated. Only the fibres of the most dorsal portion are left relatively intact. Degenerating fascicles often

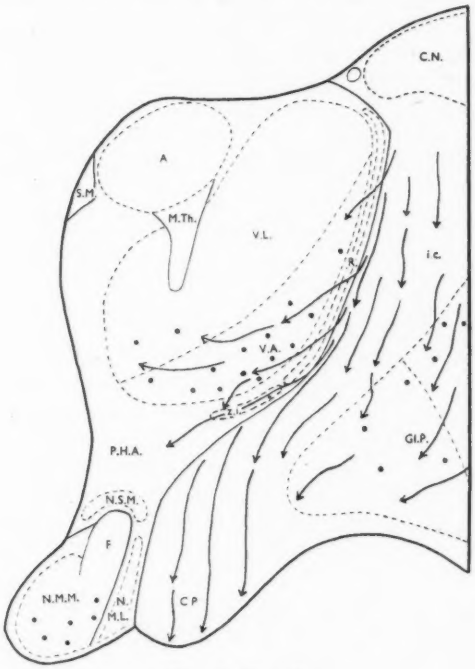

FIG. 6 (*Case* 2).

cross each other and, in one instance, a bundle of thick degenerating fibres can be traced through the whole length of the internal capsule into the cerebral peduncle. Normal fibres of the ansa lenticularis pass through in a horizontal direction, crossing the degenerating descending fascicles (Plate XIII, fig. 9). Some fine fascicles which course vertically through the thalamic fasciculus are degenerated and degenerating fibres pass into and through the zona incerta towards the posterior hypothalamic area just dorsal to the lenticular fasciculus. It was found, as in Case 1, that a large number of degenerating fibres enter the globus pallidus from the internal capsule, and enlarged terminals and fragmented fine fibres are scattered throughout both pallidal divisions, par-

ticularly close to the internal capsule. When compared with Case 1 the degenerative process does not appear to be of greater severity although any attempt at a quantitative analysis of the silver picture is of doubtful value. Degenerating fibre fascicles sweep into the nucleus ventralis anterior, some of them passing medially into the nucleus ventralis lateralis. Terminal degeneration is very marked, a feature which is in keeping with the shorter survival time in this case. The distribution of the degenerating fibres is identical in the two cases.

Some of the larger fibres which surround the ventral aspect of the caudate nucleus and which can be followed along the floor of the lateral ventricle into the anterior nucleus of the thalamus, show irregular swelling and sometimes disintegration. The fine fibres and terminals of the dorsolateral part of the anterior nucleus show some evidence of degeneration. The fibres of the wall of the third ventricle present a similar picture and, to a certain extent, the periventricular fibres and the medial border of the posterior hypothalamic area are similarly affected. The type of fibre change observed is reminiscent of the changes described by Cajal as a result of damage to the immediate neighbourhood of the axon, and the possibility therefore cannot be excluded that the degenerative change of the ventricular fibres and the degeneration seen in the anterior nucleus of the thalamus are the consequence of the hæmorrhage into the third and lateral ventricles.

Apart from the small area close to the third ventricle, the fibre pattern of the posterior hypothalamic area is intact. The medial mammillary nucleus shows severe degeneration of fine fibres and terminals, most marked at the ventral and lateral aspect of the mammillary body. Some of the fibres of the surrounding capsule are degenerating at its ventral tip. The lateral nucleus and supramammillary nucleus are normal.

Middle level (fig. 7): Some fibres of the massa intermedia show the swelling and occasional disintegration already described for the ventricular wall and must be attributed to the same cause. From the massa intermedia this type of fibre change is traceable for a short distance into the adjacent mid-line and interlamellar nuclei and also into the internal medullary lamina of the thalamus. In the nucleus ventralis lateralis large fascicles of degenerating fibres course medially and downwards and terminate in this nucleus. Some appear to reach the rostral part of the dorsomedial nucleus. Slight evidence of terminal degeneration is also found in the submedial nucleus. The thalamo-frontal radiations are intact. The most pronounced fibre change is seen in the zona incerta. Almost all the fibres are degenerated in the lateral part of this zone and terminal degeneration is very marked; medially the changes become less severe, degenerating fibres are traceable as far as the posterior hypothalamic area.

In the subthalamic nucleus the degenerative process is well defined in this case. Degenerating fascicles of fine fibres pass through its

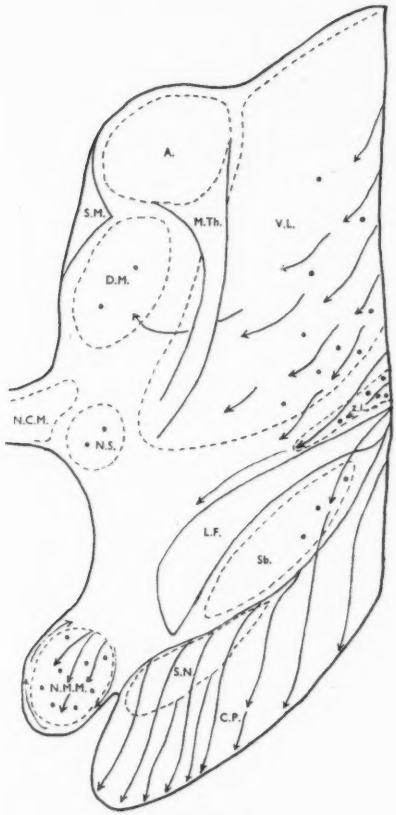

FIG. 7 (*Case* 2).

lateral half in a vertical direction. Particularly in the neighbourhood of the degenerating fascicles there is much evidence of terminal degeneration which more caudally has spread through the entire nucleus (as seen in the next level). The surrounding capsule and the fibres which form the subthalamic decussation have remained intact.

Compared with Case 1 a much greater proportion of the fibres in the fascicles which pass through the reticular zone of the substantia nigra into the cerebral peduncle are degenerated, but again no terminal degeneration can be discovered in the substantia nigra and it must be concluded that these fascicles do not make contact with the nerve cells or dendrites of this region. Fibres of the cerebral peduncle (the medial part of which only is in the section) are almost entirely degenerated. In the dorsolateral part these degenerating descending fascicles are crossed by the thick normal fibres of the ansa lenticularis. The changes

in the mammillary body are identical with those already described for Case 1.

Level 3 (fig. 8): The fibre pattern of the dorsomedial nucleus of the thalamus shows secondary changes similar to those in Case 1. Terminals sometimes reach the size of a glial cell and as many as ten are seen in one oil immersion field. Although the periventricular fibres

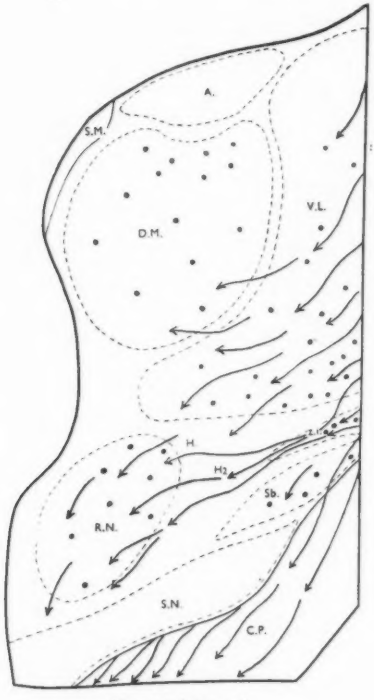

FIG. 8 (*Case* 2).

are affected by the hæmorrhage into the third ventricle, the magnocellular part shows little change. Some fascicles of degenerating fibres are traced through the nucleus ventralis lateralis and can be followed as they turn slightly upwards to enter the inferior portion of the nucleus dorso-medialis. Changes in the other nuclei of the thalamus and in the zona incerta are similar to those described for the previous level.

The fibres of the more medial field H1 are more intact than those of field H2 and, as in Case 1, degenerating fascicles of fibres course through field H2 to spread out fanwise into the small-celled division of the red nucleus (Plate XIII, fig. 6). Many fibres terminate here (Plate XIII, fig. 7), but again some degenerating fascicles appear to pass through the rostral part of the red nucleus to end either in its caudal

division or elsewhere. The capsule of the red nucleus shows a number of degenerating fibres.

Evaluation of the findings in the substantia nigra is complicated by the fact that the patient had suffered from encephalitis lethargica. In Nissl sections marked loss of melanin-containing cells is accompanied by gliosis and the few remaining nerve cells no longer contain any melanin. In the silver picture there seems to be a loss of fibres but those remaining are normal, except for some fine fibres at the dorso-lateral border which are probably passing through into the peduncle. As in Case 1 there are a large number of normal boutons terminaux on nerve cells and dendrites but no evidence of degeneration of these terminals could be established.

In the cerebral peduncle the fine fibres of the medial part are entirely degenerated, while laterally normal and degenerating fibres of a much thicker calibre are intermingled.

Degenerating fibres are found traversing the rostral part of the arcuate and parafascicular nuclei in the direction of the mesencephalic tegmentum but there is very little indication that fibres terminate in these nuclei. The centre median nucleus is intact.

In the left hemisphere of this brain the distribution of secondary fibre degeneration to subcortical nuclei following the leucotomy lesion is the same as has been described for the right side with the exception

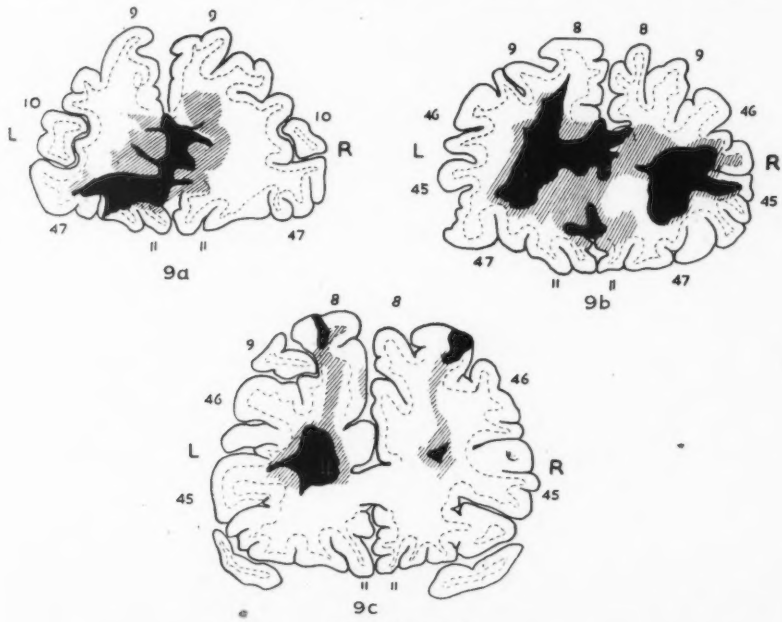

FIG. 9 (*Case* 3).

of the internal capsule and peduncle. Fascicles of the internal capsule which pass into the peduncle show less evidence of degeneration and in the left cerebral peduncle many of the thick fibres, which are degenerated in the right side, are normal.

Case 3 was a woman who at the age of 65 was admitted to hospital in a depressed, agitated, restless state of six weeks' duration with delusions and hallucinations. Leucotomy was performed four months after admission. The dorsal approach was employed, under local anæsthesia. Considerable hæmorrhage occurred during and after the left cut. The patient became slightly confused and disorientated and remained so. Double incontinence developed. On the sixteenth post-operative day she became drowsy, her temperature, pulse and respirations rose and she died in coma that evening with signs of pulmonary congestion and sugar and acetone in the urine.

Autopsy, performed some sixteen hours after death, revealed pulmonary congestion with early bronchopneumonia. The convolutions of the brain were somewhat atrophied on both sides especially in the dorsal motor and premotor regions. Traces of subarachnoid hæmorrhage were present over both temporal and frontal lobes. The arteries of the base were moderately sclerosed and atheromatous. A definite cerebellar pressure cone was in evidence. A leucotome entry mark was visible in each frontal lobe just medial to the superior frontal sulcus in area 8 at the level of the rostral tips of the lateral ventricles (fig. 9c).

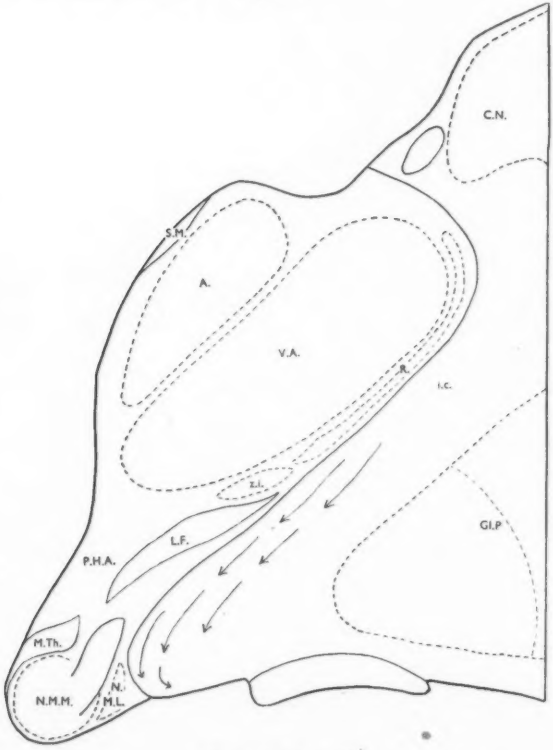

FIG. 10 (*Case* 3).

Coronal sections (fig. 9A-C) through the frontal lobes revealed a firm brown hæmorrhagic mass in the centrum ovale on both sides, which in places appeared to be continuous across the medial longitudinal fissure. The lesions involved the white matter of all the prefrontal areas of both hemispheres and faded out posteriorly in the central white matter just rostral to the head of the caudate nucleus on the left side, and at the tip of the lateral ventricle on the right side. The posterior orbital areas and area 6 were spared. The lateral ventricles were intact and there was no blood staining of the ventricular walls.

Secondary Degeneration

Anterior level (fig. 10): The entire superior part of the internal capsule is intact and only the fine fibre fascicles which swing ventromedially to form the medial part of the cerebral peduncle show severe degeneration. Laterally towards the globus pallidus evidence of fibre change diminishes and the fascicles adjacent to the globus pallidus are

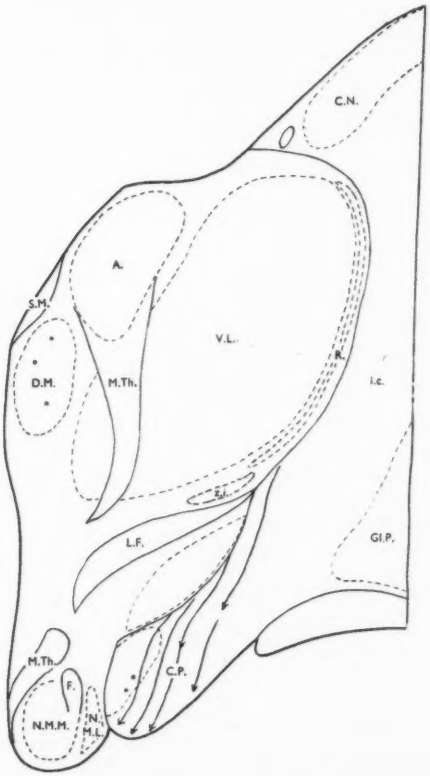

FIG. 11 (*Case* 3).

intact. The fibre pattern of the globus pallidus itself is normal. There is no clear evidence of fibre or terminal degeneration in the thalamic nuclei or the mammillary body.

Middle level (fig. 11): Some fine fibres in typical drop-like disintegration are present in the anterior part of the dorsomedial nucleus (Plate XII, fig. 5). The remaining subcortical centres are unchanged. Beading of fine fibres is very frequent; this, however, is not regarded as evidence of terminal or preterminal degeneration.

The fascicles which pass through the reticular zone of the substantia nigra into the cerebral peduncle show marked degeneration and fibres of the most medial part of the cerebral peduncle are also entirely degenerated.

Posterior level (fig. 12): The dorsomedial nucleus alone of the

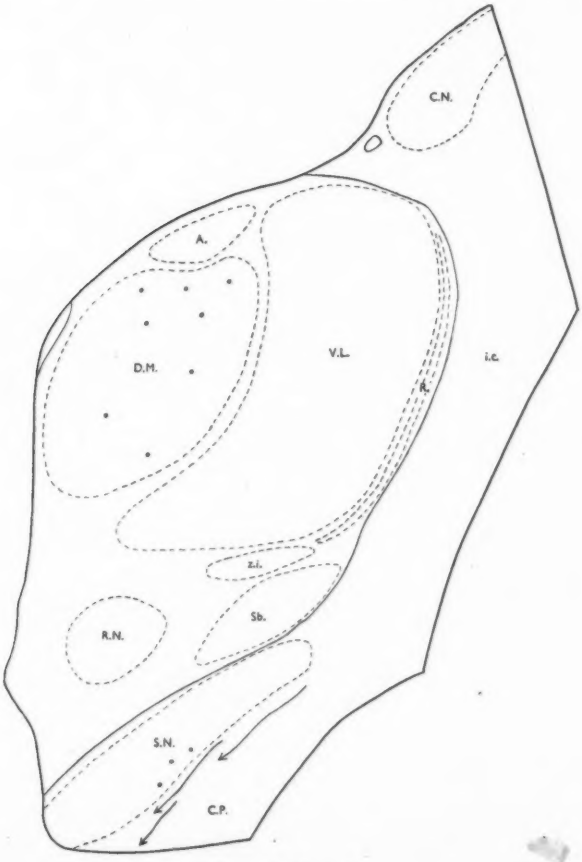

FIG. 12 (*Case* 3).

thalamic nuclei shows degenerating terminals and preterminals. Most of the fibre plexus is intact. Some of the large degenerating terminals are found as described for Cases 1 and 2 and, on closer examination, there are also fine fragmented fibres in quite considerable numbers, somewhat palely stained and refractory to impregnation (Plate XII, fig. 5).

Fine degenerating fibres pass through the substantia nigra into the medial part of the peduncle. Close to the degenerating fibres there is some evidence of terminal degeneration in the ventromedial part of the substantia nigra in this case. The melanin-containing part is intact.

In the left hemisphere of this brain some fibres are degenerated in the fascicles adjacent to the globus pallidus. Otherwise the extent and distribution of secondary fibre degeneration is the same as is described for the right side.

Case 4 was at the time of his operation a 73-year-old man with high blood pressure who had suffered from involutional depression of three and a half years' duration which had responded only transiently to courses of insulin and electric shock therapy. Bilateral prefrontal leucotomy was performed through the lateral approach. Pyrexia, confusion, restlessness and incontinence became apparent on recovery from the general anæsthesia and persisted. The patient's blood pressure remained lowered. He became stuporose on the fifth post-operative day. His blood urea content was 440 mg. per cent on the sixth day, and he died on the seventh day from uræmia.

The convolutions of the brain displayed wasting on both sides in the dorsal parts of the central and parietal regions. There was no appreciable degree of subarachnoid

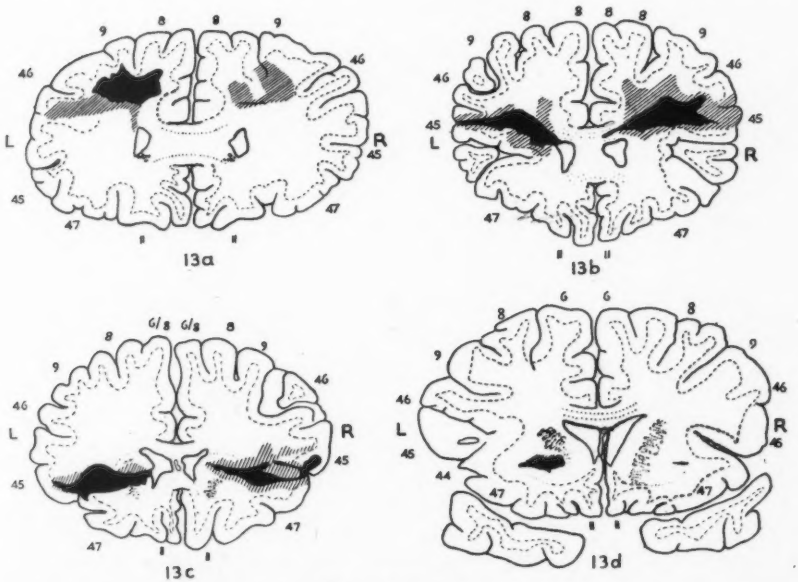

FIG. 13 (*Case* 4).

hæmorrhage or of pressure cone formation. A leucotome entry mark was visible on each side in the posterior part of the pars triangularis of the inferior frontal gyrus (Brodmann's area 45). Histological investigation revealed no evidence of infection.

Coronal sectioning of the frontal lobes showed a hæmorrhagic cleft of irregular outline where the leucotome had passed, sloping downwards and backwards from the anterior part of area 8 at its summit into the striate body at its base (fig. 13A-D). Anteriorly, the lesions were confined largely to the dorsal half of the white matter. They terminated posteroventrally in the rostral parts of the striate body, the external capsule and the anterior limb of the internal capsule. The lesion in the left hemisphere was continuous with the anterior horn of the lateral ventricle.

Secondary Degeneration (figs. 14, 15, 16)

In the subcortical nuclei evidence of terminal degeneration is confined to the dorsomedial nucleus of the thalamus (Plate XII, fig. 4), again most conspicuous at its dorsal aspect. In the internal capsule some fibres adjacent to the globus pallidus are degenerating, probably secondary to the lesion in the putamen. The most medial fifth of the cerebral peduncle shows some degenerating fibres.

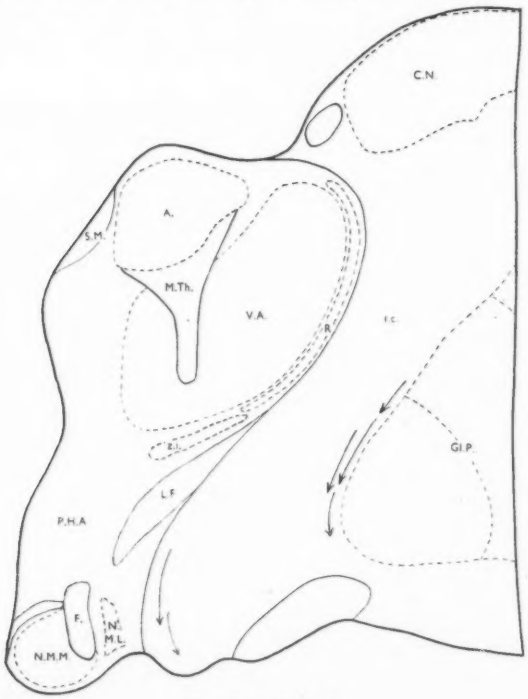

FIG. 14 (*Case* 4).

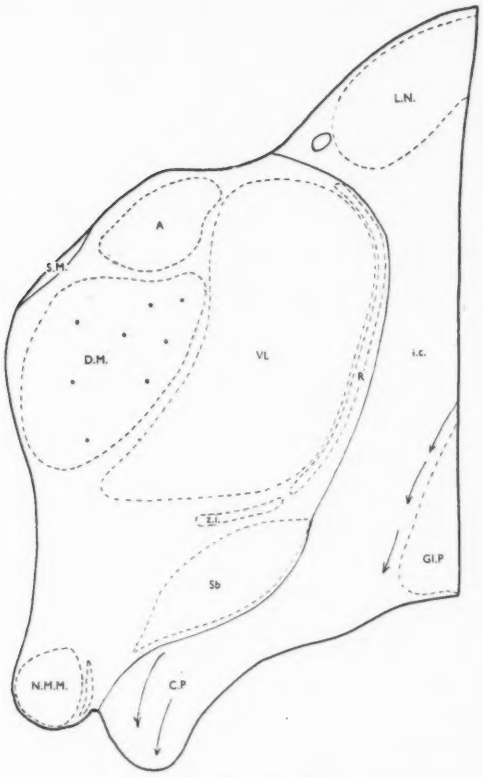

FIG. 15 (*Case* 4).

The results are similar in both hemispheres.

A series of three diagrams through the mammillary body is given to illustrate the extent and distribution of degenerative changes which are identical in Cases 1 and 2 and in both the hemispheres of each brain. The left side of Case 2 was chosen as representative of all four hemispheres (figs. 17, 18, 19, p. 287).

DISCUSSION

In evaluating the results it must be recognized that in cases with such acute lesions it is impossible to define with accuracy the limits of the leucotomy cut, and that a correlation of the cortical areas involved, with the secondary degenerative changes can only be approximate. Our knowledge of the detailed cytoarchitecture of many areas of the human frontal lobe is still incomplete and in view of the great individual variations in extent and position and even variations of the cytoarchitecture of each cortical field (in particular of area 8) a more precise localization than has been attempted would be unwise.

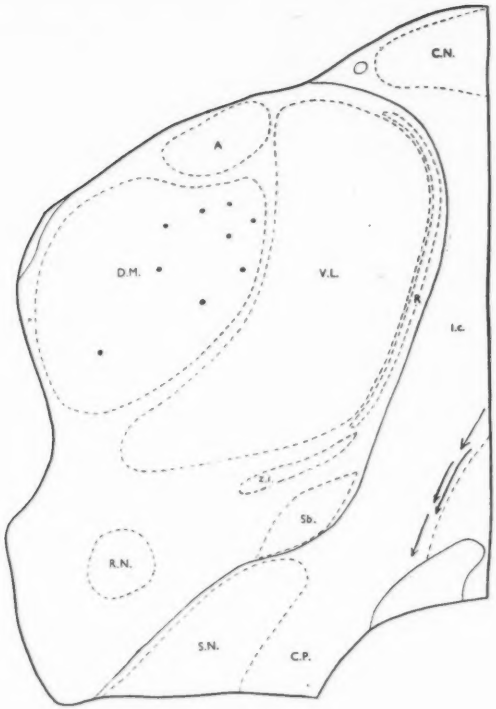

FIG. 16 (*Case* 4).

The main general inference from the present communication is that a lesion entirely confined to prefrontal granular areas (Cases 3 and 4) results in terminal degeneration in the dorsomedial nucleus of the thalamus only; the other subcortical nuclei examined being normal. If, however, as in Case 1, the lesion includes agranular cortex of the frontal lobe (areas 6 and 24) and posterior parts of prefrontal cortex which are probably dysgranular (areas 8, posterior 9, 32), terminal degeneration is found in the mammillary body, the dorsomedial nucleus and the ventrolateral group of nuclei of the thalamus and also in the globus pallidus, the subthalamus and the red nucleus. A caudally more extensive lesion (Case 2) which also severs the connexions of all the orbital areas and reaches into the head of the caudate nucleus involves the same nuclei; it does not add appreciably to the extent of the degenerative changes within these nuclei, but in the internal capsule and cerebral peduncle the degenerative changes are much more severe.

From these observations it becomes clear that the region which represents at least a part of the cortical projection area for these subcortical nuclei must lie between the most caudal extent of the lesion in

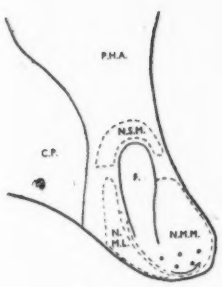

FIG. 17.

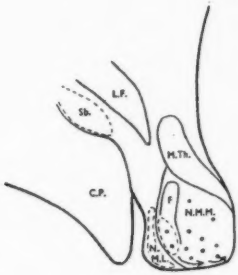

FIG. 18.

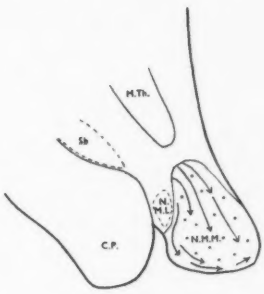

FIG. 19.

Case 1 and the posterior extent of the lesion in Case 3. They also indicate that fibres from more posterior cortical areas of the frontal lobe (Case 2) project to lower centres than those examined, a fact which points to an organization of the corticofugal fibre systems in an antero-posterior direction as has been suggested by Levin (1936) and Verhaart and Kennard (1940) for the macaque brain.

Hypothalamus.—The most striking result in this series is the anatomical evidence for a direct fibre path from the frontal cortex to the *mammillary body* in the two cases in which the lesion encroached upon the agranular cortex of the dorsal convexity. It is the first anatomical evidence for such a connexion and corroborates Ward and McCulloch's (1947) report that strychninization of area 6 fires, amongst other hypothalamic centres, the mammillary body.[1]

The technique employed shows with great clarity the distribution of the degenerative process. The rostral part of the mammillary body is almost intact; more caudally, signs of degeneration begin in the ventral part of the medial nucleus and in its lateral division and gradually spread until in the most caudal part of the mammillary body, which only contains the medial nucleus, almost the entire fibre plexus of this nucleus and fibres of the surrounding capsule are in process of degeneration.

The localization of the degenerative process is the same in the two cases and is bilateral in both.

Contrary to Ward and McCulloch's findings, the lateral and supramammillary nuclei are not affected, nor is there any evidence that fibres from the frontal lobe terminate in the *posterior hypothalamic* area, although in Case 2 fibres from areas 45 and 47 have been interrupted in

[1]The term mammillary body as used here includes only the medial mammillary nucleus and its lateral division, which is that part of the mammillary complex which is separated by a fibre capsule from the two accessory nuclei, the lateral mammillary nucleus (nucleus intercalatus of Le Gros Clark) and the supramammillary nucleus. It is of interest that some workers regard the supramammillary and lateral mammillary nuclei as a condensation of cells of the posterior hypothalamic area (all three large-celled nuclei) not to be included in the nuclei of the mammillary complex.

addition to other areas. It may be noted that Ward and McCulloch (1947) recorded that the posterior hypothalamic area responded to strychninization of areas 6a, 45 and 47.

The possibility that a hæmorrhage into the third ventricle in these cases might have disturbed the periventricular fibre system and thus have caused the degenerative changes within the mammillary body has not been overlooked, but it can safely be excluded if the site of the primary lesion is considered in relation to the results. In both Cases 2 and 3 the periventricular fibre system is not entirely normal but only Case 2 (where the lesion extends into area 6) shows degeneration in the mammillary body. When the primary lesion remains confined to the prefrontal areas, as in Case 3, the mammillary body is intact although the periventricular fibres show pathological changes. Finally, Case 1 demonstrates that the two findings are not necessarily associated, for here an intact periventricular system is combined with degeneration in the mammillary body.

It has frequently been pointed out that the hypothalamus must be under some degree of cortical control and it has been suggested that this control is exerted by indirect fibre connexions. It has been shown experimentally in Marchi studies, for example, that connexions from various areas of the frontal cortex to these relay nuclei exist. Hitherto, however, there has been no anatomical evidence for a direct connexion to the mammillary body. Mettler, after ablation of area 6a in the macaque monkey, was able to trace fibres from the internal capsule through the zona incerta no farther than the posterior hypothalamic area, but, as the Marchi method does not show the fine unmyelinated terminals, it is possible that these fibres extend further. The pathway indicated by Mettler's experiments appears to be the most plausible route for fibres reaching the mammillary body from the frontal cortex, but since no direct continuity in the sections examined could be traced, other pathways or perhaps other projection areas cannot be entirely excluded, such as, for instance, the cingular gyrus, which is known to contribute to the fornix through fibres which perforate the corpus callosum.

The functional significance of the mammillary body is unknown. In man the medial mammillary nucleus reaches its greatest relative size and highest degree of differentiation (Le Gros Clark, 1938), which is presumably not entirely due to the influence exerted by the hippocampal cortex and conveyed by the fornix to the mammillary body. Mettler has correlated the apparently close relationship of area 6 to autonomic function with the direct hypothalamic projection of this area.

Thalamus.—That the *anterior nucleus* projects to the cingulate gyrus is well established by animal experimental work (Le Gros Clark and Boggon, 1933; Walker, 1938; Lashley, 1941; Rose, 1947). In studies of human leucotomized brains Meyer, Beck and McLardy confirmed that there is a system of projection in man similar to that described in

lower mammals, namely that the antero-medial element projects to the rostral cingulate gyrus and the antero-ventral element to its caudal part. No reciprocal cortico-fugal connexion from the rostral cingulate gyrus could be established in our material. Although in Cases 1 and 2 the primary lesion interrupted almost all fibres which arise in area 32 and those of the anterior and medial portion of area 24, no definite terminal degeneration was demonstrated in any of the elements of the anterior thalamic nucleus. The changes described in Case 2 must be attributed to the ventricular hæmorrhage. These findings are well supported by recent anatomical and physiological observations in macaques, for Ward (1948), after ablation of area 24, could not trace fibres into any of the thalamic nuclei in Marchi preparations, while Bailey and von Bonin and their co-workers (1944) found that after strychninization of areas 24 and 32 the anterior thalamic nucleus did not respond. It was fired, however, after strychninization of areas 23 and 29.

Rose, Woolsey and Jarcho (1947) recently recorded responses mainly from area 23 after electrical stimulation of the mammillary body and the authors suggested that with the relative enlargement of the antero-ventral element in primates, together with the development of the granular area 23—the latter (the posterior cingulate gyrus) is the main receptive area for impulses from the hypothalamus which are then relayed to the effector area 24. The antero-medial element is much reduced in man and it may be suggested that its projection to the anterior cingulate gyrus has become relatively insignificant; this would account for the absence of (or possibly the inability to demonstrate) a reciprocal cortical connexion.

The course, distribution and termination of the cortico-fugal fibres to the *nucleus ventralis anterior, nucleus ventralis lateralis* and the *nucleus reticularis* of the thalamus are indicated in the diagrams of Cases 1 and 2. Lesions restricted to the prefrontal areas only (Cases 3 and 4) demonstrate that there is no cortical connexion to these nuclei. The amount of degeneration observed suggests a fairly heavy projection from the cortical areas involved to these thalamic nuclei, more marked to the nucleus ventralis lateralis (to that part which projects to area 6) than to the nucleus ventralis anterior. The reticular nucleus almost certainly receives corticofugal fibres, although the evidence for terminal degeneration is obscured by the large numbers of degenerating fascicles passing through it. The cortical fibres are of fine and medium calibre and they reach these nuclei in fascicles through the internal capsule.

The only human case reported by Minckler, Klemme and Minckler (1944) confirms that fibres from area 6 pass into the thalamus. Their patient died seven months after extirpation of the premotor area for the relief of Parkinsonian tremor, and Swank-Davenport staining showed that "the descending premotor fibres within the internal capsule give off a large component which enters the superolateral aspect of the thalamus."

Summarizing the results of experimental ablations of different areas of the frontal cortex in macaques, opinion appears to be unanimous that area 6 sends fibres to the nuclei ventralis anterior, ventralis lateralis and to the reticular nucleus (Levin, Verhaart, and Kennard, Hines). However, also after ablation of prefrontal areas (areas 9 and 8 of Vogt) Hirawasa and Kato find Marchi degeneration in these nuclei and Mettler (1947) after a primary lesion almost restricted to area 9 encountered Marchi degeneration in the reticular nucleus, the anterior portion of the ventrolateral group and the nucleus ventralis ventralis. Levin reported similar findings after ablation of various areas of the prefrontal cortex. The present writer could not find any degeneration in cases with lesion restricted to prefrontal areas which included the rostral part of areas 9 and 8, but area 9 particularly is much more extensive in the human brain than in the macaque. Moreover, Brodmann's areas 8 and posterior 9 correspond to Economo's area FC which is mainly dysgranular, and therefore if such corticothalamic fibres exist they may arise from dysgranular areas, which are not true prefrontal cortex. Levin concluded that in the macaque the most extensive frontothalamic system arises from the convexity of the frontal lobe, i.e. from area 9, and that fibres from areas 6 and 4 form a smaller part of the efferent system to the thalamus. This last suggestion is of interest for in the human brain degenerative changes in the ventrolateral group did not appear to be more severe when more posterior portions of area 6 were severed.

Norman, comparing experimental findings with his human case of atrophy of the frontal lobes, suggests a progressive shifting of the thalamic projection in a frontal direction. Also, according to Walker, the thalamic projection to area 6 becomes progressively larger as one ascends the phylogenetic scale. It is probable that the same holds good for the corticothalamic system, as observed by Hirawasa and Kato when comparing the corticofugal connexions of area 4 of the cat with those of the monkey brain.

The results in the present communication emphasize the great extent and importance of the cortical projection to the ventrolateral group of the thalamic nuclei in the human brain.

The *dorsomedial nucleus* is the only thalamic nucleus which shows terminal degeneration in all cases, including cases in which lesions were restricted to the prefrontal areas. The results of experimental anatomical (Le Gros Clark, 1932; Mettler, 1935, 1947; Levin, 1936; Hirawasa and Kato, 1935) and physiological (Murphy and Gellhorn, 1945) studies in lower mammals and monkeys had previously suggested the existence of a prefronto-dorsomedial connexion for the human brain. Fibres have been described as reaching the dorsomedial nucleus by two routes: the one traversing the ventrolateral group of thalamic nuclei from the posterior limb of the internal capsule; the other via the anterior limb of the internal capsule in close relation to the septal region,

reaching the dorsomedial nucleus by way of the internal medullary lamina. Apparently fibres from the prefrontal areas take the latter route and those from areas 8 and 6 the former.

Conditions appear to be similar in the human brain. In cases with prefrontal cuts (when the posterior limb of the internal capsule and the ventrolateral group of the thalamic nuclei are free from degeneration) no degenerating fibres were seen on their way to the dorsomedial nucleus although there was terminal degeneration. It might be assumed that fibres from the prefrontal cortex reach the dorsomedial nucleus by the same route as has been described by Le Gros Clark and Mettler, which would parallel the thalamo-frontal radiations. In cases with more posterior cuts additional cortical fibres traverse the ventrolateral group to pass into the dorsomedial nucleus and degeneration within the nucleus is somewhat more severe. In some areas of the dorsomedial nucleus the degenerative process appears to be more severe than in others, but this could not be related with certainty to any of the cortical areas involved in the primary lesion. For instance, in all cases the dorsal aspect of the dorsomedial nucleus showed terminal degeneration most prominently in an area which sometimes includes but is not restricted to the magnocellular part. This same region projects to area 45 and to the orbital areas of the frontal lobe and the possibility of a reciprocal corticofugal connexion would be a very plausible explanation. Case 1, however, in which the orbital areas were not interrupted, rules out any such interpretation. Moreover, in Case 2, in which fibres from the orbital areas are cut, and the periventricular fibres also affected by the hæmorrhage into the third ventricle, the magnocellular part of the dorsomedial nucleus showed no more change than is observed elsewhere in the dorsomedial nucleus. Thus a point-to-point localization as has been demonstrated for the dorsomedial-prefrontal projections (Meyer, Beck and McLardy, 1947; Freeman and Watts, 1947, etc.) could not be established in the material examined. The amount of terminal degeneration is always surprisingly small. This insignificance of the reciprocal corticofugal projections to the dorsomedial nucleus, particularly if compared with the more massive cortical projection to the ventrolateral group, raises interesting questions of function.

In all cases there is evidence that fibres from the frontal cortex terminate in an area just ventral to the dorsomedial nucleus which is labelled *nucleus submedius* in the diagrams. Although few authors agree on the boundaries and terminology of the nucleus submedius, the area must be intimately associated with the dorsomedial nucleus and, as Meyer, Beck and McLardy have pointed out, the two nuclei are apparently closely related in their cortical projection. Only in man has a corticopetal connexion been advocated and there is no record of a corticofugal projection. Meyer, Beck and McLardy connect area 8 with the submedial nucleus together with the adjacent portion of the dorsomedial nucleus. Freeman and Watts described a projection from

the nucleus submedius to area 46. The connexions of both these areas are severed in all 4 cases described, and thus a reciprocal fibre connexion is indicated.

There was no evidence in this material that fibres from those frontal areas which were involved terminated in the parafascicular, arcuate or centromedian nuclei of the thalamus. In the 2 cases in which lesions involve the anterior part of area 6, degenerating fibres traverse the rostral portion of the parafascicular and arcuate nuclei towards the tegmentum. Mettler, after ablation of the whole of area 6 in macaques, describes Marchi degeneration in the subfascicular nucleus (nucleus parafascicularis according to the terminology followed in this paper) and also after ablation of posterior area 6 and area 4s in the arcuate and centromedian nuclei. Since in none of the cases described in this communication the whole of area 6 or area 4s is involved, they are unsuitable for comparison.

Connexions of the frontal cortex with extrapyramidal nuclei.—The connexions between the frontal cortex and *globus pallidus* have been the subject of much controversy. Anatomical and physiological studies have established a corticostriatal connexion, mainly from the suppressor bands of the cerebral cortex to the caudate nucleus and, lacking convincing anatomical evidence for a direct pathway, it had been assumed that cortical influences upon the globus pallidus act by way of the caudate nucleus or the substantia nigra (Bucy, 1942) until Dusser de Barenne, Garol and McCulloch (1942) by means of the method of physiological neuronography revealed a direct pathway from area 6 to the external segment of the globus pallidus.

Experimental anatomical work in macaques and baboons using the Marchi technique has so far not given a satisfactory answer to the question of a direct frontopallidal connexion.

According to some reports (Mettler, 1947; Hirawasa and Kato, 1935) there is a projection from the frontal cortex to the globus pallidus; fibres originate in areas 6, 8 or 9; area 8 apparently contributes fibres to the medial segment and area 6 to the external segment of the globus pallidus.

On the other hand Levin (1944), in reviewing the cortico-pallidal connexions, expressed doubt as to their extent and origin, and he agrees with Verhaart and Kennard (1940) who regard the degenerating fibres seen in the globus pallidus after coagulation of area 6 as "deflected fibres of passage" from the internal capsule, reasoning that in lower mammals part of the globus pallidus is lying within the internal capsule. Considering the present findings it seems quite definite that in cases with lesions extending into agranular cortex of the frontal lobe (Cases 1 and 2[1]) degenerating fibres terminate in the globus pallidus. The

[1]It should be remembered that Case 2 was a case of post-encephalitic Parkinsonism, but the present writer is satisfied that the changes seen are not connected with this chronic condition.

extent of the cortical projection is considerable. Again it is impossible to determine precisely the localization of the degenerative process, and the relationship to the cortical areas involved.

In the two cases (Cases 1 and 2) in which the leucotomy lesion extends into the agranular cortex of the frontal lobe, fronto-fugal fibres terminate in the *zona incerta*, in *Forel's fields* and in the *red nucleus*. These fibres take their course through the posterior limb of the internal capsule into the zona incerta to enter the small-celled part of the red nucleus by way of Forel's field, particularly H_2. Fibres terminate chiefly in the small-celled part of the red nucleus, which is of more recent phylogenetic origin and most highly developed in man. Its capsule, which consists of afferent and efferent fibres, also shows some degeneration.

Experimental research of earlier workers has supported the contention that a connexion from the frontal cortex (areas 6 and 4) to the zona incerta, Forel's fields and the red nucleus exists. In recent investigations on macaques, however, there is no agreement as regards the precise cortical area which projects on to these nuclei. Mettler (1935) describes degeneration in the zona incerta, in Forel's field and in the red nucleus after ablation of prefrontal areas (8, 9 and 10) and area 6, but in his 1947 report he finds that only area 4s sends fibres to the red nucleus and none of the areas rostral to it. This result is again not supported by Hine's experiment after removal of the strip area. After ablation of area 6a Verhaart and Kennard traced degenerating fibres no further than the zona incerta and Forel's field, whereas Hirawasa and Kato, after ablation of prefrontal areas (8 and 9), assume that at least part of the fibres which pass through the zona incerta and Forel's field terminate in the red nucleus. The present results clearly indicate that granular areas of the prefrontal lobe do not connect with any of these centres.

Degenerating fascicles of fibres from the internal capsule pass through the *subthalamic nucleus* into the cerebral peduncle and there is evidence that some of these or their collaterals terminate in the subthalamic nucleus close to the descending fibres. Only its lateral part is affected anteriorly; at more posterior levels the whole nucleus becomes involved. Le Gros Clark (1932) demonstrated a conspicuous cortico-subthalamic connexion after a lesion involving the frontal pole of the rat. In the human brain Meyer, Beck and McLardy saw patches of gliosed descending fascicles passing through the subthalamic nucleus after lesions which involved agranular cortex. Otherwise a cortico-fugal connexion between the subthalamic nucleus and any part of the frontal cortex has been denied (Levin, 1944; Mettler, 1947; Verhaart and Kennard, 1940; Hirawasa and Kato, 1935).

Levin (1944) in his review on cortico-fugal connexions regards the *fronto-nigral* tract as established in man and a number of animals, its main origin being from the precentral region. According to observa-

tions on Marchi material, fibres terminate in the middle and caudal portion of the substantia nigra, the rostral reticular zone being unaffected. Minckler, Klemme and Minckler (1944), however, concluded from their findings in a human brain that termination of fibres in the substantial nigra from area 6 is open to question and they suggest that "the area 6 component of the cortico-nigral bundle in human material would appear to be far less than in the monkey."

In the cases described here the substantia nigra was not sufficiently studied to be able to make a valuable contribution to this problem. In 3 cases only the rostral portion of the substantia nigra was examined. Degenerating fibres were seen passing through it on their way into the cerebral peduncle but there was no evidence that fibres terminate in the reticular zone of the substantia nigra, which is in accordance with Marchi studies.

In the fourth case (Case 3) a more caudal portion of the substantia nigra shows some terminal degeneration in the ventromedial part, close to the degenerating fibres of the cerebral peduncle. This is a suggestive finding but before being accepted it will have to be supported by more evidence.

The varying extent of the leucotomy lesion in the 4 cases described is impressively reflected in the *internal capsule* and *cerebral peduncle*. Here fibres of different cortical origin have a different position which gives an indication of the cortical areas severed by the cut. The topographical arrangement of fibres from the frontal cortex passing downward in the internal capsule and cerebral peduncle has been worked out experimentally by Levin (1936) in the macaque monkey. According to him, the most medial part of the cerebral peduncle is occupied by fibres from the prefrontal cortex, adjacent to it (in transverse section) are those from area 8 and these are adjoined laterally by fibres from areas 6, 4s and 4.

As far as the prefrontal cortex and area 6 are concerned our results confirm this arrangement also for the human brain. The question of the existence of a prefronto-pontine tract has recently been reviewed by Meyer, McLardy and Beck (1948). They conclude from leucotomy material that there is some evidence in favour of a prefrontal origin of fibres descending into the cerebral peduncle and pons, a view, not supported by Kirschbaum and von Bonin (1947) who report no changes in the cerebral peduncle even when the cortical injury extends into area 6. According to these authors the prefronto-pontine tract arises exclusively from the precentral motor cortex.

The 2 cases with lesions anterior to area 6 reported in this paper provide some evidence that fibres of the fronto-pontine tract originate rostral to the premotor region. The leucotomy cut in Case 3 has resulted in severe degeneration of fibres of the medial segment of the cerebral peduncle. In Case 4 in which the lesion is more anterior, sloping downwards and backwards into the orbital areas and striatum

only very few fibres in the medial cerebral peduncle are degenerated. Comparison of the 2 cases suggests that fibres of the fronto-pontine tract may arise in areas anterior to the premotor cortex, but not necessarily in granular prefrontal cortex. A more detailed study of the position of the descending fibres in the internal capsule and cerebral peduncle, particularly the origin and termination of the prefronto-pontine tract, will be the subject of a later publication.

Summary

(1) Brains of patients with a short survival time after leucotomy have been examined with a silver method to trace corticofugal fibres to their termination in subcortical nuclei.

(2) After leucotomy lesions restricted to prefrontal areas surprisingly few fibres from the severed areas terminate in the dorsomedial nucleus of the thalamus. Experimental findings asserting that the prefrontal cortex projects to other thalamic or extrapyramidal nuclei are not confirmed for the human brain.

(3) When the leucotomy lesions extend into the white matter which underlies dysgranular and agranular cortex of the frontal lobe, terminal degeneration is present in the mammillary body, the dorsomedial and ventrolateral group of nuclei of the thalamus, the globus pallidus, zona incerta, Forel's field, red nucleus and subthalamic nucleus.

(4) It has been possible to demonstrate that the cortical fields projecting to these centres are confined to the rostral part of Brodmann's area 6 and to dysgranular areas of the frontal cortex such as Brodmann's areas 8 and posterior 9 (Economo's area FC).

(5) Fibres from the frontal cortex which terminate in the mammillary body may represent the anatomical pathway previously suggested by Ward and McCulloch on physiological evidence.

(6) The extent and importance of frontal projections to the ventrolateral group of thalamic nuclei in the human brain is emphasized. A projection from the rostral cingular gyrus to the anterior nucleus of the thalamus could not be demonstrated.

(7) Of the extrapyramidal nuclei the finding of a direct cortico-pallidal pathway is of particular interest.

(8) Fibres from the frontal cortex were seen to terminate in the red nucleus after lesions which certainly exclude areas 4 and 4s.

(9) Degeneration of fibres of the fronto-pontine tract in the most medial part of the peduncle was present after lesions anterior to the premotor cortex.

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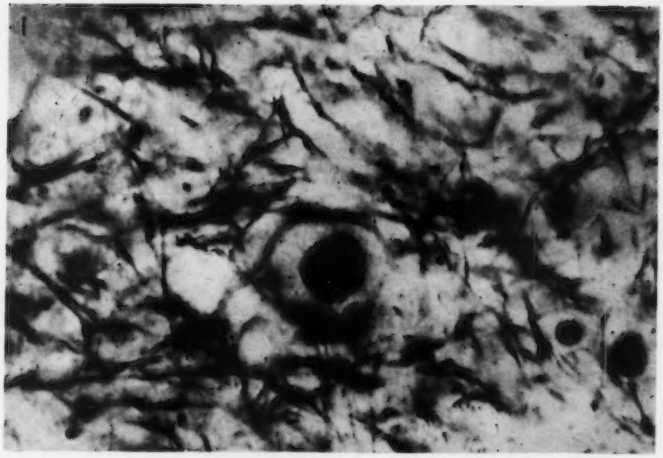
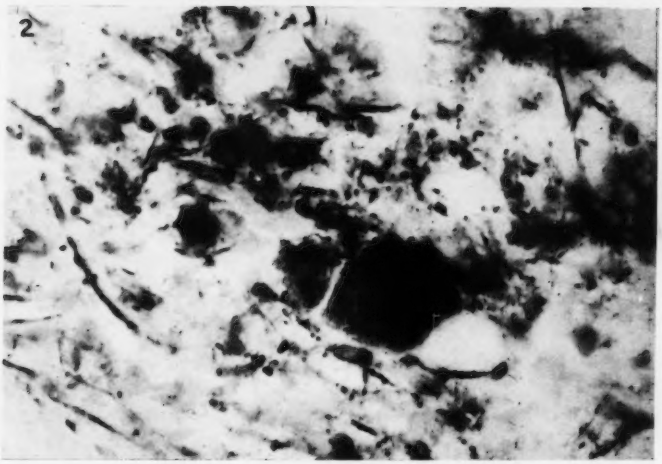
ABBREVIATIONS

A	= Anterior nuclear group.	N.M.L.	= Nucleus mammillaris lateralis.
C.N.	= Caudate nucleus.	N.S.M.	= Nucleus supramammillaris.
C.P.	= Cerebral peduncle.	N.S.	= Nucleus submedius.
D.M.	= Dorsomedial nucleus.	P.H.A.	= Posterior hypothalamic area.
F	= Fornix.	Put.	= Putamen.
Gl.P.	= Globus pallidus.	R.	= Reticular nucleus.
H_1	= Forel's Field H_1.	R.N.	= Red nucleus.
H_2	= Forel's Field H_2.	Sb.	= Subthalamic nucleus.
I.C.	= Internal capsule.	S.M.	= Stria medullaris.
L.F.	= Lenticular fasciculus.	S.N.	= Substantia nigra.
M.Th.	= Mammillo-thalamic tract.	V.A.	= Nucleus ventralis anterior.
N.C.M.	= Nucleus centralis medialis.	V.L.	= Nucleus ventralis lateralis.
N.M.M.	= Nucleus mammillaris medialis.	Z.I.	= Zona incerta.

PLATE XI.





All plate figures are photomicrographs of silver sections.

FIG. 1.—The normal fibre plexus of the medial mammillary nucleus. × 1,000.

FIG. 2.—Degeneration (drop-like disintegration) of the terminal fibre plexus in the caudal part of the medial mammillary nucleus in Case 1, fifteen days after leucotomy. The lesion involves agranular cortex of the frontal lobe. × 1,000.

To illustrate article by Margaret Meyer.

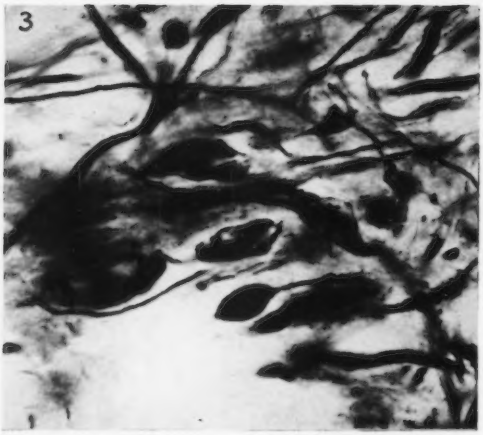


FIG. 3.—Degenerating fibres (irregular swellings with centre portion still intact) and enlarged terminals in nucleus ventralis lateralis of the thalamus seven days after leucotomy, Case 2. × 1,440.

FIG. 4.—Enlarged terminal on a nerve cell of the dorso-medial nucleus of the thalamus in Case 4, seven days after leucotomy. × 800.

FIG. 5.—Disintegrating fine fibre in the dorso-medial nucleus of the thalamus sixteen days after leucotomy, Case 3. × 1,000.

To illustrate article by Margaret Meyer.

PLATE XIII.

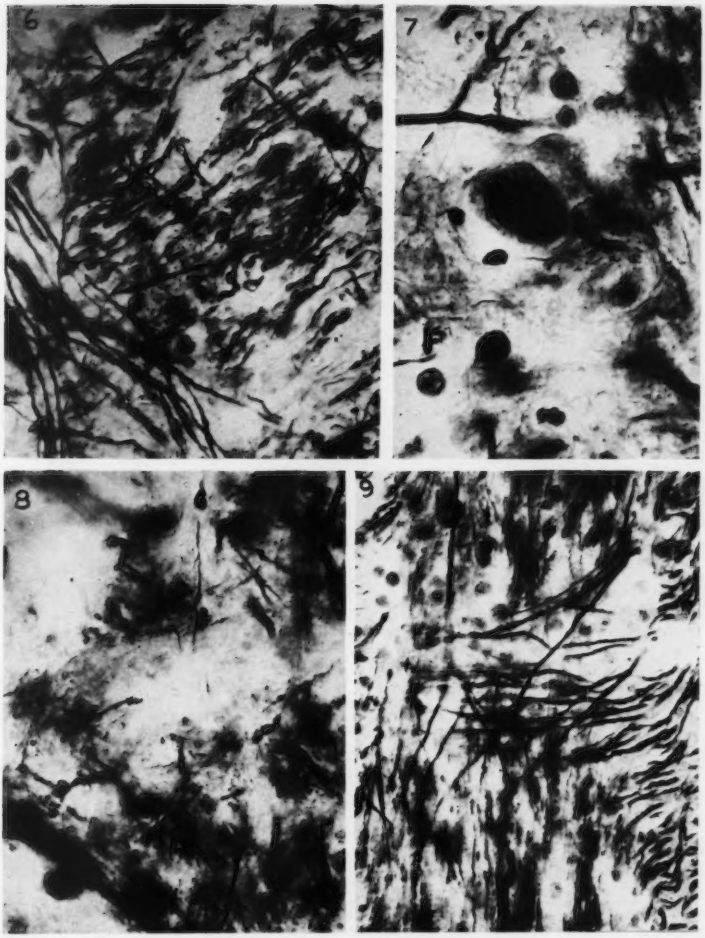


FIG. 6.—A degenerating fibre fascicle in the red nucleus which is crossed by normal fibres. Case 2, seven days after leucotomy. × 640.

FIG. 7.—Three degenerating terminals on a nerve cell of the red nucleus. Case 2, seven days after leucotomy. × 1,000.

FIG. 8.—Disintegrating fine terminal fibres in the globus pallidus fifteen days after leucotomy, Case 1. × 800.

FIG. 9.—Degenerating descending fibre fascicle in the internal capsule, the normal fibres of the ansa lenticularis are passing across. Case 2, seven days after leucotomy. × 640.

To illustrate article by Margaret Meyer.

THE RELATIVE SYMPATHETIC CONTRIBUTION TO INDIVIDUAL ROOTS OF THE BRACHIAL PLEXUS IN MAN

BY

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IN an earlier paper, published in this Journal, relating to the distribution of sympathetic fibres in the brachial plexus in man it was stated that "the relative sympathetic contribution to each root, based on the cross-sectional areas of the rami, is at present under investigation" and attention was directed to the importance of this information (Sunderland, 1948). This enquiry has been completed and the results form the subject of this paper.

THE ENQUIRY

The observations were made on four autopsy specimens which were, in each case, obtained as follows. The roots of the brachial plexus were severed beyond the scalene muscles and the sympathetic trunk divided below the superior cervical ganglion and distal to the second thoracic ganglion. The vertebral column and cord were sectioned down the mid-line. A block of tissue containing the cord, nerve roots, vertebral artery and sympathetic trunk was then removed, care being taken to preserve the normal relationships of the various structures to one another. A standard histological technique was employed to prepare each block for examination. The block was fixed in 5 per cent formal saline and then decalcified by the rapid decalcification method using formic acid (Russell, 1939). This was done in order to facilitate the exposure and dissection of the sympathetic plexus associated with the vertebral artery as the latter ascended through the foramina of the transverse processes of the cervical vertebræ. This technique ensured that any sympathetic twigs passing from the vertebral plexus to the roots of the brachial plexus would not be missed. The sympathetic twigs linking each root of the brachial plexus to the sympathetic trunk and vertebral plexus were carefully identified and isolated by dissection. A segment was taken from each twig, dehydrated in the ascending grades of alcohols, cleared in cedar wood oil and embedded in paraffin. Transverse sections were cut at 10 microns and stained with hæmatoxylin and eosin. The sections were enlarged on a microprojector to a constant magnification and drawn. The cross-sectional area of each sympathetic twig, which may be accepted as a measure of the number of the contained sympathetic nerve fibres, was then measured on the charts with a planimeter. The cross-sectional areas of all the sympathetic twigs passing to the plexus were totalled and the combined cross-sectional area of the twigs to each root was then ex-

pressed as a percentage of this. These values may be accepted as a measure of the relative fibre contribution to each root.

It should be noted that the cross-sectional area of a funiculus provides only an approximate, and not a precise, measure of its fibre content since the relationship is affected by such factors as the amount of intrafunicular connective tissue and any shrinkage occurring during the preparation. The sympathetic twigs were composed of funiculi that contained very little connective tissue. Though some shrinkage was inevitable the histological picture suggested that this was minimal in degree. In an attempt to minimize any error so introduced, material from the same and different subjects was subjected to precisely the same technique so that any shrinkage occurring during the process would be substantially the same in each preparation; it is unlikely that minor differences in the size of the funiculi, all of which were very small, would have imposed significant individual differences in this regard. For these reasons it is felt that the shrinkage and connective tissue content of the funiculi were not such as to preclude the general thesis that the cross-sectional area of a funiculus represents a reasonably accurate reflection of its fibre content.

Observations

(1) There were no pure white rami. The myelinated pre-ganglionic fibres were always combined with post-ganglionic fibres in mixed funiculi and the two types of fibres were so intermingled that it was impossible to obtain separate cross-sectional area measurements for each.

(2) The fifth, sixth and seventh cervical nerve roots may receive a contribution from the vertebral plexus but not the eighth cervical and first thoracic.

(3) Mixed rami to the eighth cervical nerve root were observed in two of the four specimens investigated.

(4) Neurons were observed in the rami to the fifth cervical (1 specimen), seventh cervical (1 specimen) and eighth cervical (1 specimen) nerve roots.

(5) The percentage contribution of sympathetic fibres to each nerve root is given in Table I with information as to the proportionate supply from the sympathetic trunk and vertebral plexus. It should be noted that, in the case of two and four specimens of the eighth cervical and first thoracic nerve roots respectively, this value includes both the pre- and the post-ganglionic components though a separation was effected where possible. The pre-ganglionic contribution to the eighth cervical was not large in the two specimens in which it was present and though measurements were not possible it did not appear to exceed 10 to 25 per cent of the cross-sectional area of the mixed rami. In the case of first thoracic nerve roots respectively, this value includes both the pre-greater and in the mixed rami represented approximately 50 per cent

of the cross-sectional area. If the post-ganglionic supply to the individual roots is calculated on this basis the relative percentage contribution of these fibres to each root in the four specimens becomes:

Specimen	1	2	3	4
Fifth cervical nerve ...	6·4	5·8	9·0	1·2
Sixth cervical nerve ...	10·4	8·5	27·4	17·2
Seventh cervical nerve ...	15·2	25·8	20·5	18·2
Eighth cervical nerve ...	44·0	31·6	27·8	35·1
First thoracic nerve ...	24·0	28·3	15·3	28·3

Possible errors in these estimates were:

(i) Some very fine twigs to the spinal nerve roots from the vertebral plexus may possibly have escaped detection or have been inadvertently destroyed when exposing the vertebral artery though every effort was made to avoid this. This possible, though unlikely, source of error could have been eliminated by serially sectioning the material but such a technique was contra-indicated owing to the necessity of obtaining true transverse sections of the twigs in order to accurately measure their cross-sectional areas. We are confident that no direct communications between the spinal nerve roots and the sympathetic trunk were missed.

(ii) No rami passed directly from the second thoracic ganglion to the first thoracic nerve root. Though the small contribution from the second thoracic nerve to the first contains post-ganglionic sympathetic fibres which reach it from the second thoracic ganglion via the second thoracic nerve, these were so mixed with the somatic nerve fibres of the communication that it was not possible to assess the cross-sectional area of this component. For this reason it was not possible to include in the percentage sympathetic fibre content of the first thoracic nerve those post-ganglionic fibres that had reached it from the second thoracic nerve.

(iii) Errors in estimating the pre-ganglionic content of the mixed rami. The estimate of the relative proportion of pre- and post-ganglionic fibre content of mixed funiculi was such, however, that though the value for the pre-ganglionic component could not have been greater, it may have been less. For this reason the estimates given are on the conservative side.

Conclusions

Regardless of the possible sources of error in the estimation of the relative percentage contribution of the post-ganglionic fibres to each root of the plexus the following generalizations would appear to be justified with reference to this morphological feature.

(1) All roots of the brachial plexus conveyed post-ganglionic sympathetic fibres peripherally.

(2) The relative percentage contribution of sympathetic fibres to each individual root of the plexus varied.

(3) (i) In any individual specimen there were proportionately more post-ganglionic fibres in the eighth cervical root (25 to 45 per cent)

TABLE I.—THE CROSS-SECTIONAL AREA AND PERCENTAGE CONTRIBUTION OF THE SYMPATHETIC FIBRES TO INDIVIDUAL ROOTS OF THE BRACHIAL PLEXUS. THE AREAS ARE IN SQUARE INCHES AT AN AREA MAGNIFICATION OF 2,100

Specimen and source of sympathetic fibres	SPINAL NERVE								
	Fifth cervical	*Sixth cervical*	*Seventh cervical*	*Eighth cervical*			*First thoracic*		
				*N.M.**	*Mixed*	*Total*	*N.M.**	*Mixed*	*Total*
(1) Sympathetic trunk ..	0·55	0·89		3·77			1·35	1·41	
Vertebral plexus ..			1·30						
Total	0·55/6·0%	0·89/9·6%	1·30/14·0%	3·77/40·7%		3·77/40·7%	1·35/14·5%	1·41/15·2%	2·76/29·7%
(2) Sympathetic trunk ..	0·50	0·42	1·09	0·32	3·03		0·42	4·05	
Vertebral plexus ..		0·31	1·13						
Total	0·50/4·4%	0·73/6·5%	2·22/19·7%	0·32/2·8%	3·03/26·9%	3·35/29·7%	0·42/3·7%	4·05/36·0%	4·47/39·7%
(3) Sympathetic trunk ..	0·53	0·98	1·22	1·65			0·52	0·79	
Vertebral plexus ..		0·65							
Total	0·53/8·3%	1·63/25·7%	1·22/19·3%	1·65/26·0%		1·65/26·0%	0·52/8·2%	0·79/12·5%	1·31/20·7%
(4) Sympathetic trunk ..	0·12	1·65		0·62	3·45		0·28	4·89	
Vertebral plexus ..			1·75						
Total	0·12/1·0%	1·65/12·9%	1·75/13·7%	0·62/4·9%	3·45/27·0%	4·07/31·9%	0·28/2·2%	4·89/38·3%	5·17/40·5%

* = Non-myelinated.

than in any other though the first thoracic component (15 to 30 per cent) may approach it closely. Woollard (1931) reported that "the caudal roots of the plexus receive a greater number of post-ganglionic fibres" though no details were provided. The present findings, however, are not in agreement with Woollard and Weddell's observation (1935), which was based on the examination of a single specimen in which no attempt was made to discriminate between pre- and post-ganglionic fibres, that "over twice the number of sympathetic fibres were contributed to the eighth cervical compared with any other root."

(ii) There were proportionately fewer post-ganglionic fibres in the fifth cervical root (1 to 9 per cent) than in any other.

(iii) The post-ganglionic sympathetic contribution to the sixth (8 to 27 per cent) and seventh (15 to 25 per cent) cervical roots occupied an intermediate position with that of the latter usually exceeding the former. A substantial number of post-ganglionic fibres accompanied these two nerve roots peripherally.

(4) Forty to 70 per cent of the post-ganglionic fibres in the brachial plexus were contained in the lower trunk.

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ADEQUATE STIMULI

(With Special Reference to Cutaneous Nerves)

BY

J. H. PARSONS

In spite of the vast amount of work expended on the investigation of cutaneous sensations, the subject is still in a chaotic condition.

The early experiments of Goldscheider, von Frey, and others, are well described by Sherrington in Schäfer's "Textbook of Physiology" (II, 920, 1900), and show that the distribution of the receptors is punctate; and that isolated touch-, warm-, cold-, and pain-spots can be mapped out in any area of the skin.

The after-effects of division of cutaneous nerves in man were studied by Head and Rivers (1905–8). Their theory of protopathic and epicritic nerves was criticized—on the results of their own experiments—by Trotter and Davies (1909–13), Boring, and others; and finally and exhaustively by Walshe (1948).

Few theories have more corroborative evidence than the duplicity theory of vision; and it was perhaps not surprising that an ophthalmologist should have been deeply impressed by Head's theory. I therefore applied it, in somewhat modified form, to visual sensations in my Bowman Lecture (1925); and further extended the modified theory to embrace other sensations in my "Introduction to a Theory of Perception" (1927).

Much light has been thrown on the transmission of impulses in nerves by Keith Lucas, Adrian, Bronk, Hartline, and others; and Gasser and Erlanger have analysed the compound changes in nerve trunks, determining the fibre components involved and suggesting their relation to sensory activities.

The electrophysiological study of sensory function reveals fascinating data for the explanation of that most perplexing problem—how nerve impulses of the simple character revealed by the experiments of Adrian and others can convey "messages" of great complexity and variety to the brain. In this connexion the researches of Ragnar Granit (1947) on the electrical potentials in the retina and optic nerve cannot be overlooked. It is dangerous to draw any but tentative conclusions from analogies; but in the retina and optic nerve there are two types of end-organs, the rods and cones, in immediate relationship with bipolar cells (which are analogous to posterior root ganglia), and through them with retinal ganglion cells (which resemble the second neurone of the sensory path). The optic nerve, which is composed almost entirely of

axons of the ganglion cells, is really an extracerebral internuncial tract —the whole retina being an isolated portion of brain.

If the analogy has any validity, it is certain that very complex reactions take place in the end-organs themselves; for photochemical changes of qualitative variety occur in the rods and cones, and initiate nerve impulses which must carry specific messages.

On the more purely anatomical side the researches of Woollard and Weddell, and their co-workers (1940–48) have clarified the characters, distribution and destinations of the nerve fibres, thus providing data of greater precision for the physiologist.

The greatest advance in our knowledge of the physiology of sensations, however, is coeval with Head's work. It is contained in Sherrington's epoch-making "Integrative Action of the Nervous System" (1906). It may seem strange to seek such information in a book primarily devoted to the study of reflex action. But, phylogenetically, *sensation is the causa causans of action;* and this is so whether we predicate a primitive undifferentiated sentience—"mind it may be of such elementary grade as to be difficult for us to picture its operation" (Sherrington)—to lowly organisms or not. Anyhow, the tropisms are motor responses to stimuli. At a slightly higher stage there are many examples of localized responses to stimulation (*vide infra*). At a still higher stage reflex actions are fully developed.

All these responses are *purposive;* and in the present state of knowledge it is not only undesirable, but unwarranted, to ignore teleological speculations (cf. Sherrington, p. 237). In fact, it is almost impossible to do so; and those most averse from them frequently indulge in them unwittingly. "Each animal has experience only of those qualities of the environment which as stimuli excite its receptors; it analyses its environment in terms of them exclusively" (Sherrington, 1906, p. 318). The extero-receptive receptors can be classified according to a physiochemical or to a physiological scheme. The latter deals with them more satisfactorily; and "the key to the physiological classification lies in the reaction which is produced" (p. 319). "Adaptation has evolved a mechanism for which one kind of stimulus is appropriate, i.e. *the adequate stimulus*"; and "every adequate stimulus must obviously be a natural form of stimulation" (p. 12).

End-organs are the specially differentiated receptors for specific adequate stimuli; and the natural form of stimulation is always a *receptor-pattern* of less or greater complexity, in which probably invariably more than one adequate stimulus is involved. Only thus can the responses integrate into a *meaning*—witting or unwitting[1]—which is the drive to the purposeful *reactive-pattern*. Hence, probably invariably, the stimuli give rise to *plurireceptive summation*, not only

[1]May I commend the use of the word "unwitting," selected after much thought by Rivers, to describe actions performed without consciousness, though ill-described as "subconscious" or "unconscious"?

of the same, but also of different modality. Examples of chemical and mechanical reinforcement have been proved as low down as in Actinians and the cat-fish. Sherrington, indeed, goes so far as to say that "the rank of a 'centre' in the neural hierarchy is the degree to which paths from separate loci and of different receptive modality are confluent therein" (p. 313).

Plurireceptive summation of impulses derived from end-organs of different modality is almost as difficult a problem as that of body and mind. The skin might well be regarded as a suitable organ for its investigation; for here are distributed end-organs of several different modalities, viz. for touch, heat, cold, pain and pressure. The investigations which have been made hitherto have adopted the methods of the physical sciences; i.e. the dissociation and isolation of a single modality. These researches early demonstrated the punctate distribution, and apparent isolation, of touch, warm, cold, and pain spots. There was not, however, that precision and constancy of isolation which is characteristic of physical experiments; doubtless in part due to dealing with living structures in a perpetual state of change.

It was the examination of these punctate phenomena which led Cattell and Hoagland (1931), Sarah Tower (1935, 1940), and others to try to identify *"the physiological unit of sensory reception"* (Walshe, 1948, pp. 40, 55–6). Walshe regards it as "probable that the sensory unit consists of all the end-organs supplied by a single posterior root fibre" (p. 44). Apart from the ambiguity of the term (which at first sight suggests a unit of sensation—only to be justified by the questionable mathematics of Fechner), what is apparently meant is an *anatomical* unit of sensory reception. Walshe bases its existence on the false analogy with Sherrington's motor unit of function, the motoneurone.

The motoneurone is a useful abstraction, having probably no more real existence than a simple reflex—"a reflex detached from the general nervous condition is hardly realizable" (Sherrington, 1906, p. 117)—or a pure "sensation." A motor anatomico-physiological unit, however, has much more pragmatic value than the theoretical sensory unit. For every motor neurone is the end of a common path; whereas a sensation is an abstract entity of that plurireceptive summation which is called a percept.

Moreover, as Sherrington points out (1906, p. 176), "the distribution in the skin of any afferent root does not correspond with the receptive field of any cutaneous reflex." How, therefore, can Walshe's sensory unit have any pragmatic value?

Of all the sensations derived from the skin under normal conditions few are due to punctate stimulation, but these are of immense importance; for, *inter alia*, they are the foundation of local signature and of "two-point discrimination."

Walshe (1948, p. 39) dismisses two-point discrimination with the curt statement that they are "judgments based upon sensory material."

It is remarkable that so distinguished a psychologist as Rivers allowed so much loose phraseology to creep into his and Head's writings. Discrimination is, indeed, a judgment, and therefore ultimately a function of the higher centres; but it depends upon the "minimum separabile" of two points stimulated at the periphery. The retina is a group of "glorified warm-spots" (Sherrington, 1906, p. 323); and it is the retina which teaches us most about punctate discrimination.

The highest degree of discrimination is visual. There is overwhelming evidence that it depends fundamentally upon the fineness of the mosaic of end-organs—rods and cones—at the site of stimulation. The "minimum visual angle"—the angle subtended at the nodal point of the eye by two points of light which are just recognizable as two—agrees with the size and dispersion of the foveal cones. But there is good evidence that it also depends upon the complete isolation of the afferent path from the cones through the retina to the external geniculate body. Visual acuity rapidly diminishes in passing from the fixation point towards the periphery of the retina. This is due, not only to the greater dispersion of the cones and the interpolation of increasing numbers of rods, but also to the synaptic association of several rods and cones with a single bipolar cell. In this respect there is analogy between macular vision and active touch; "the macula corresponds to the tip of the finger" (Mach).

These facts, however, are by no means the whole explanation of discrimination. Sherrington "found osmic-stained nerve fibres of 4μ diameter visible to the naked eye for both myself and other workers in the laboratory (1906, p. 186). This is called "contour discrimination," and by it the minimum visual angle is reduced from nearly one minute of arc for two stars to less than ten seconds of arc. The explanation is to be sought largely in spatial induction.

Even more illuminating from the tactile point of view is the fact that the foveal cones, so precisely isolated for punctate discrimination, are still capable of working in unison for other purposes. It was first shown by Ricco (1877) that for the foveal region, i.e. up to 40 or 50 minutes visual angle, "at the threshold of sensibility the quantity of light entering the eye is constant; or, in other words, the light intensity and the area of the retinal image are reciprocal functions; or, the product of the area into the light intensity is constant" (Parsons, 1934, p. 130).

It is clear, therefore, that here, in spite of the precisely limited one-way traffic demanded by a high degree of discrimination, the machinery for a spatial spread of the response is also present. It may be accounted for by synaptic communications in the layers of the retina: if so, there must be some process of inhibition to account for the absence of spread in precise discriminatory responses.

It is less easy to account for such inhibition in the case of cutaneous two-point discrimination; yet, however much this is finally a judgment

carried out by higher centres, these must be provided with the discrete data necessary for judgment. Instead of an immediately proximal bipolar cell forming a synapse with an immediately proximal ganglion cell, the posterior root cell is far away and the second neurone is within the central nervous system. It seems, therefore, that inhibition must be carried out by some peripheral mechanism, such as may be possibly provided by axon-reflexes and antidromic impulses. Le Gros Clark, in his Robert Boyle Lecture (1947), suggests that the power of localization and ability to discriminate between two closely applied stimuli depend on the pattern of the peripheral arborization of a single fibre, and the degree to which it overlaps with the arborizations of adjacent fibres; for it has been shown that the area covered by the terminal network of a single *pain* fibre in the skin corresponds closely with the degree of two-point discrimination. In any case, the inhibition is *active*, and not merely passive; and therefore may depend upon some much more complicated activity in the central nervous system itself, comparable with the active inhibition of antagonistic muscles.

If one accepts the existence of touch-, warm-, cold-, and pain-spots in the skin it would seem that all should possess the discriminative capacity; and we have seen that this is true for touch and pain. Is it also true for warm and cold spots? Would two compass points of exactly the same temperature as the skin, applied with a minimum of pressure, arouse two-point discrimination? The experiment would be difficult, and probably could be done only by two thermopiles as compass ends. Probably there would be no such discrimination.

It would seem, therefore, to follow that so-called tactile discrimination is impossible without deforming pressure. This has already been stated by Sherrington (1906, p. 227), confirmed by Trotter (1909, 1913), and reaffirmed by Blake Pritchard, and Walshe (1948, p. 16). Two-point discrimination is therefore not a simple matter of "touch" *or* "pressure" *or* "pain," but a much more composite affair. It is hence desirable that when one is referring to simple tactile sensations some such terms as *"haptic"* should be used; similarly *"thermal"* for warmth and cold; and *"algesic"* for pain.

If one considers the *adequacy* of stimulation, i.e. the nature of the stimulation which is normal to the normal intact animal and produces normal responses, these experimental stimuli are not normal. Would the lightest contact produce a haptic response above the threshold? This cannot be tested by von Frey's hairs, whose criterion is "grammes per square millimetre"—"grammes and millivolts as such mean nothing to the organism" (Walshe, 1948, p. 34). Such stimuli in real life are like those of the flea, each of which may be subliminal; but they can be rendered effective in time by repetition and summation, and in space by induction; as in Sherrington's striking experiment of inducing the scratch reflex by drawing the edge of a card over the skin (p. 185). But here again, the response is not a simple haptic response, but a complex

one—commonly called itching or tickling; even with or without a conscious response it may result in motor action.

It is, however, as purely haptic a response as one can elicit; and the complexity is due to plurireceptive summation of successive stimuli of the same modality. It shows therefore that light contact *can* produce a haptic response; and that two-point discrimination is due to plurireceptive summation of different modalities.

All these examples, and many others which might be adduced, to show that the analysis of a *perception* results in the manufacture of elementary theoretical *"sensations"*; and that the whole process of sensory perception consists in the plurireceptive summation of abstract sensations of either the same or different modality.

Is it not possible that, impressed by the brilliant success of the analytic method in the much simpler domain of physical science, biologists have attached too much importance to the results of their own analytical experiments, endowing them with a quasi-immutable validity which they do not deserve? One hesitates to advance a speculative philosophical argument; but, if there is any truth in the Gestalt Theory (or Holism) that the whole is greater than the algebraic sum of its parts, it would follow that analysis is a more destructive process than has been realized, and that the properties of the isolated part, if indeed it exists other than as an abstraction, are very different from the "part" as incorporated in the "whole." Even in physics analysis leads to hypotheses which possess great validity, but are mutually incompatible; e.g. the wave and quantum theories of light.

What goes on in the spaces between the spots—spaces which reveal nothing to consciousness? Are they like the interspaces between the rods and cones, or like the head of the optic nerve (the "blind spot")? In ordinary vision the blind spot is completely filled in and is only revealed consciously by perimetric observations. Similar gaps of pathological origin in the retina produce similar "negative scotomata"; whereas others produce "positive scotomata," i.e. consciously appreciated gaps in the visual field. A newly acquired lesion will cause a positive scotoma, though it may be so small or so peripheral as to require special methods for its manifestation. Time and the scarring process may turn the positive into a negative scotoma; but by no means always. The difference from the nerve head may be due to the absence of receptors there; so it would seem more probable that the gaps in the haptic field are of central origin, resembling the relative suppression of the peripheral field of vision when attention is directed to the fixation point.

The *inadequacy* (in more senses than one) of the particulate method is lamentably exemplified in Head and Rivers's investigations of the thermal responses. As Boring (1916) says, it is one thing to map out an area for cold or warm spots, and quite another thing to find the same ones a second time and not to find new ones (cf. Goldscheider,

Waterston, and others). How often do human beings experience punctate, or even approximately punctate thermal stimuli in normal life? Do they ever experience them except from objects at such temperature as to make them nocuous, and therefore painful?[1]

Trotter (1941), in his Victor Horsley Memorial Lecture, emphasized the importance of inclining to "the use of ideas of a definitely biological type" and "a constant and docile reference to experience." If physiologists had not been unduly afraid of teleological arguments the existence of two large groups of cold- and warm-blooded animals might have given them pause. The homothermal animals, to which man belongs, have a temperative above that of the environment, varying only within narrow limits; but it does vary, and therefore thermal stimuli, hot or cold, act diffusely or locally upon the skin, the temperature of which also varies.

It was perhaps due to Trotter's great clinical experience as a surgeon that he realized the supreme importance of this fact; so that he and Davies were able to show that *normally innervated skin is insensitive to temperatures within 5° C. of the skin temperature* (1913).

The thermal responses, far more than the haptic, reveal that the body, even in a state of repose, is bombarded with stimuli derived not only from extero-, but also from proprio- and intero-ceptors; and it is upon this low-toned, but very complex, background that the excitatory stimuli fall. This *cœnæsthesis* is comparable to muscle tonus. In the normal conditions of activity, however, the cœnæsthesis has already been disturbed by countless impressions, and the background is permeated with their after-effects. It is upon this sensitive film that the new picture is developed.

The noci-ceptors, whose response is *pain*, differ fundamentally from the tango- and thermo-receptors. Whereas the latter respond only to specific forms of excitation, the former seem to respond to such different modes of stimulation as mechanical, thermal conductive, thermal radiant, chemical, and electrical; and are therefore *anelective* (Sherrington, 1906, pp. 228, 318). Moreover, they are scattered in the greatest profusion all over the skin.

Further, it is now generally accepted that they are the fine naked nerve fibres distributed among the superficial epithelial cells of the skin; and that they have no end-organs. Trotter (1941) strongly supports this view, attributing the anelective sensibility and emphatic response to the lack of insulation (p. 67). He thinks that "the general tendency of all forms of sensation yielded by regenerating nerve to develop a certain resemblance to pain reminds us that regenerating fibres resemble

[1] In the ordinary use of the word we *never* experience a punctate stimulus. Even the image of a point source of light, e.g. a star, on the retina is a "circle of diffusion." If we *do* experience a punctate stimulus, it must be of the nature of a quantum.

pain fibres in a lack of complete insulation" (p. 69). If this were literally true there must be some mechanism to prevent a condition of perpetual pain. In reality, however, the fibres end between the epithelial cells, which constitute their protective covering, and to all intents and purposes their end-organs, thus resembling a more primitive form of cutaneous end-organs.

Trotter (1941) had already pointed out that pain has as an essential function the signalling of potential injury rather than the notification of actual damage, and that pain can be elicited by stimuli below the level of intensity at which injury to the tissues is produced. How then is the pain produced? Surely the explanation is that all the stimuli which cause pain are of such a nature and intensity as to cause adequate injury to the epithelial cells, so that the nerve fibres are not only exposed, but submitted to the irritation of histamine-like substances. If this is so, it is easy to understand how painful stimuli act as alarm-clocks. Moreover, deeper injuries may expose the naked fibres distributed to specific end-organs and so cause pain; thus accounting for the ambiguity surrounding the question as to whether pain is caused by higher intensities of stimulation of haptic and thermal end-organs.

In association with varying cœnæsthetic conditions it may also explain the divergent views on the threshold values for pain. According to Head, "pain is always a high threshold sensation"; and to Trotter, "remarkably high" (1941, p. 66). Sherrington (1906, pp. 227–8) gives some striking comparisons; and Walshe (1948, p. 34) says that "pain has a threshold appropriate to its special purpose"—a statement which conveys the real truth.

There are differences of opinion as to whether the excitation of nociceptors by feeble stimuli gives rise to sensations of touch. Minimal degrees of pin-prick are said to be interpreted as light touch; but Woollard, Weddell & Harpman found that areas of skin containing nothing but pain fibres and their endings did not give this response.

The most conspicuous feature about pain as compared with other sensations is its emotional response—it is charged with affective tone. It gives an imperative warning, and is prepotent in causing motor responses. Walshe (loc. cit., p. 35) says "there is nothing primitive about pain"; such a statement can only be justified by the ambiguity of the word "pain." "Physical pain is the psychical adjunct of a protective reflex" (Sherrington, "Man on his Nature," 1941, p. 286): it is therefore the psychical expression of danger in animals endowed with mind. "In animal forms which partake of mind its noci-ceptor organs pertain to sentience, and provoke 'pain' " (p. 286). Trotter (1941, p. 69) says that "primitive sensibility of all kinds we may suppose to have been like pain in us": it would perhaps be more accurate to say that primitive sentiency "is probably a vague, undifferentiated touch, in which awareness of a foreign body includes mechanical, thermal,

and chemical elements, to which singly or combined, there is choice only of two responses, positive or negative, characterized sensorily as pleasant or unpleasant, motorially as movement towards or movement away" (Parsons, 1927, p. 7).

From this undifferentiated sentience the process of evolution leads to the *partial* segregation of the different sensory modalities; but the "unpleasant" stimulation is of such prepotent significance for survival that in higher animals the response is pain.

The ambiguity of the word "pain" is shown in the fact that the opposite of this kind of pain is not precisely described by the word "pleasure." Neither is there a convenient antithesis of pleasure: the best term is perhaps "unpleasure" (cf. *Unlust*). The haptic and thermal stimuli of the skin conduce in high degree to the pleasant and unpleasant perceptions derived from it. The unpleasant ones become painful if the stimulation is too strong, too extensive, or unduly prolonged. It would therefore not be surprising if cutaneous pain possessed haptic and thermal elements; nor would it be surprising if stimulation of low degree of noci-ceptors produced sensations of touch, or warmth or cold. Not only so, but may not these haptic and thermal abstractions be less specific than has been thought? Does either occur psychically in the absence of the other? Perhaps the common and less well-defined term *"touch"* describes the facts best after all; but, if so, the term must be reserved for passive touch as opposed to active touch. Active touch involves ego-centric factors as well as extero-centric; and its complexity is well exemplified by the problem of "local signs" (see especially Sherrington, 1918). (Collected Writings, 1939, pp. 105–115; and Parsons, 1927).

It is generally admitted that phylogenetically sensations have progressed from a vague *"perception brute"* to a symphony of specific sensations, which in the presence of mind fuse into perceptions. The character and degree of the differentiation which occurs varies both phylogenetically and ontogenetically. In some species smell is prepotent, in others vision; and individuals also vary similarly, though less obviously. In all these cases there is a residuum of more or less failure of differentiation, and also of respectively atavistic or "habitual" relapse. These sensory phenomena are not "things," like molecules, which can be precisely separated into particulate elements. Their investigation must be by approach from a different standpoint from that of the physical sciences. The brilliant results of using "ideas of a definitely biological type" cannot be better illustrated than in Sherrington's work.

While phylogenetic temporal sequence from the undifferentiated to the differentiated is generally admitted, the ontological persistence of both in the individual is denied—at least in the form of two systems, protopathic and epicritic, such as Head and Rivers advanced. Yet

Ariens Kappers (1920), from comparative anatomy of the nervous systems of vertebrates, showed strong evidence in favour of the theory. There are few people adequately equipped to criticize this work; and it may be as fallacious as Gaskell's origin of the vertebrates from the king-crab. Head's duplicity theory of cutaneous sensations cannot be upheld in its crude form; but it may adumbrate a truth which may be more important for psychology, individual and social, than for physiology.

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SENSATION AND VOLITION

BY

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I. Introduction.
II. Origin of Movement.
III. Origin of Voluntary Movement.
IV. Clinical Aspects of Voluntary Movement.
V. Summary.

I. Introduction.

"Sensation may be defined as the first mental effect of a physical cause. Volition may be defined as the last mental cause of a physical effect."

Bertrand Russell: "Human Knowledge, Its Scope and Limits."

At the present time clinical and physiological teaching on many aspect of brain function seems concerned more with analysis than synthesis. Thus in the textbooks we find "The Motor System" described as a functional and isolated whole; while many pages later we find "The Sensory System" similarly treated. Each has its detailed diagram of important landmarks and tracts. This method of instruction has practical advantages but suggests very strongly, sometimes overwhelmingly so, that a real separation between the two systems exists. Many will admit to thinking of the motor pathways as "something that goes down" and the sensory pathways as "something in the opposite direction." Most of us will have no positive feeling that these pathways cannot function separately.

The impression that remains after study of the texts, and to an even greater degree, the illustrations of contemporary articles, is of blocks of tissue and groups of cells hatched and dotted upon diagrams of the brain, each collection warring with its neighbours for local predominance and authority. The so-called "angular" gyrus possesses some specific properties which the "supramarginal" gyrus can but inaccurately mimic. A discrete lesion of the angular gyrus, we learn, can be easily detected by a series of arithmetical tests and by observing how the patient puts his clothes on and so forth. We believe this because of the dots and lines in a textbook diagram, and we are not critical of ourselves when, in the post-mortem room, we find a lesion of several inches in each dimension occupying the posterior half of the hemisphere.

In this connexion we are soon led to the subject of "myeloarchitectonics" and "cytoarchitectonics." It has been assumed by many authorities, for years, that cytoarchitectonics "proved" the subdivisions correct. It has been implied, if not boldly asserted, that cell type would

run parallel with function. Thus Fulton (1934) writes: "The motor area is defined histologically as the region of the cortex containing in its fifth layer the large cells of Betz which give rise to the pyramidal pathways. It should be emphasized that the limits of motor area are determined by its cellular structure and not by its electrical excitability." We are told that pyramidal cells "of the large type" being, as it was supposed, most abundant in the motor and "pre-motor" areas—areas which on laboratory stimulation most commonly gave rise to movements of a pattern vaguely similar to that of daily usage in the normal subject —were responsible for voluntary movement. They "initiated" it. When it was noted that lesions, pathological or experimental, of the medullary and spinal pyramidal pathways caused defects in voluntary movement of a type similar to those caused by local motor area lesions, it was presumed that the spinal pyramidal tract fibres were the axons of the pyramidal cells of the motor cortex.

Lashley and Clarke (1946) have recently criticized the conception of local well-defined cytoarchitectonic groupings and do not confirm all the findings of the earlier work, so familiar and superficially attractive, of Brodman, von Economo, Foerster and the Vogts. They find that though there are here and there areas with a relative preponderance of one type of cell, classified by empirical standards, there are no sharply defined areas of special cells correlated with motor function. Ferrier (1886), one of the earliest stimulators of the cortex, said: "The areas have no exact line of demarcation from each other, and where they adjoin stimulation is apt to produce conjointly the effect peculiar to each." A further fact still, which appears to have been disregarded possibly because of its inconvenience in a tidy theory, is that of Grunbaum and Sherrington (1901) who found in the chimpanzee "in the frontal *and occipital* regions respectively, portions of the cortex which, under faradization yield conjugate movements of the eyeballs."

Research on the relationship of the giant cells of Betz, the motor cortex and the origin of the pyramidal tract, as studied by various techniques and after various lesions has been critically reviewed by Walshe (1948). Two points relevant to the present discussion are clear. First, only a small fraction of the pyramidal tract fibres are derived from their traditional source, the giant cells of Betz. He points out: "There are some three-quarters of a million pyramidal fibres to be accounted for, many of them fine and unmedullated, and 30,000 Betz cells cannot account for them."

Secondly, ablation of the motor cortex produced loss of but one-fifth of the pyramidal fibres, and we may recall the finding of Monakow (1917) that to cause total loss of the fibres of one pyramidal tract he had to remove all the contralateral cortex.

It is a reasonable impression to retain from these facts that the pyramidal tract has a far wider field of origin than the "histologically defined

motor cortex." A comparable cortical sensory pattern of a wider distribution than that of the classical "sensory cortex" is shown in the demonstration of Walker (1938) that the thalamo-cortical projections proceed to terminations all over the cortex (fig. 1).

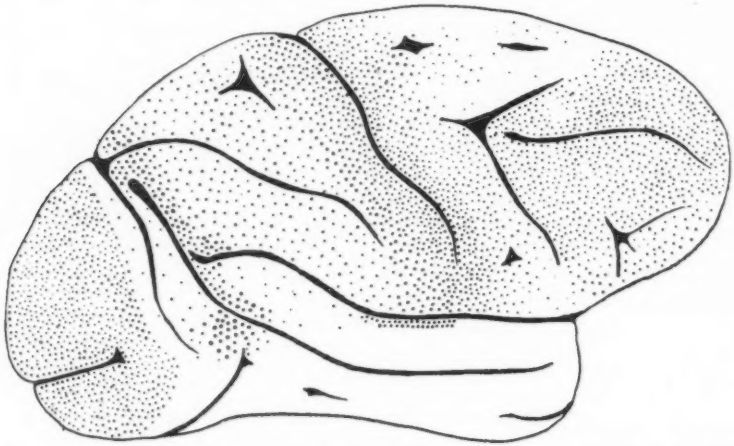

FIG. 1.—Cerebral hemisphere of macaque showing relative density of thalamo-cortical projections to various regions of cerebral cortex. (Walker, Primate Thalamus, 1938.)

Reverting to the views of the older workers (Bastian, Horsley, Head) Penfield and Ericksen (1941) support the idea of a sensorimotor cortex, the area to include parts of the frontal and parietal regions. Bastian (1886) remarks: "Each 'special' Perceptive Centre . . . may, at times, and according to the nature of the stimulus, form the starting point in 'sensorimotor' Acts." The diagram of Penfield and Boldrey (fig. 2) is helpful in emphasizing the overlap of motor and sensory functional areas.

It is no longer satisfactory, therefore, to suggest that from a block of tissue narrowly confined to an anatomically defined "motor area" issue impulses which of themselves are adequate to provide the brilliant repertoire of everyday voluntary movements with which we either as observers or performers are familiar. For the area, anteriorly at least, is ill-defined and its projection only a fraction of a common path responsible for the transmission of whatever the nerve impulses may be which subserve the total range of voluntary movement.

The motor cortex must therefore be dethroned from its supposedly supreme position in the exercise of voluntary movement, and placed in humbler circumstances. Authority for such action is ready to hand. Sherrington (1906) stated: "Another instance of an internuncial path is the so-called 'pyramidal tract' characteristic of the nervous system. It

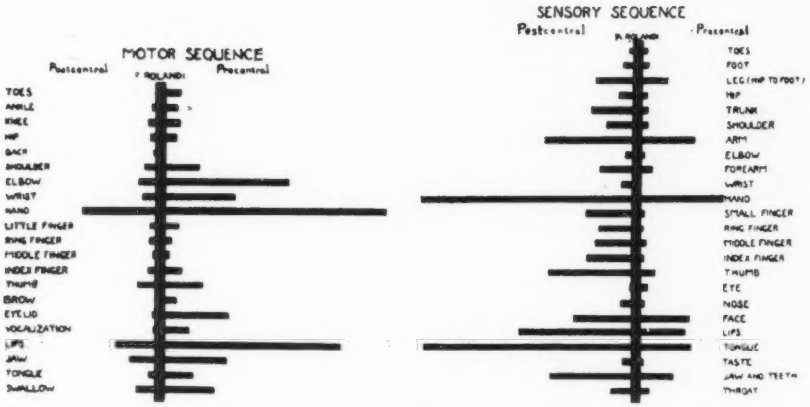

FIG. 2.—Charts of motor and sensory sequence. (Penfield and Boldrey, *Brain*, **60**, 1937.)

furnishes a path of internuncial character common to certain areas that have arisen indirectly from various receptors of various species and are knitted together in the cerebral cortex." Walshe (1948) makes clear the same point in a manner easier for clinicians to comprehend. "It is essential, therefore, to stress the importance of the idea of the receptor system as initiating and directing willed movements in contrast to the widespread assumption that we may usefully contemplate the physiology of movement as starting *ab initio* from a mechanically conceived 'keyboard' in the motor cortex. The point of view derives from a still earlier assumption, namely, that we may regard the highly artificial phenomena ensuing upon electrical stimulation of the cortex as reproducing the normal activity of the brain in initiating and directing willed movements, or at least as not differing from this in a degree or manner calling upon us for any intellectual exegesis. The willed movement, the 'precurrent' reaction as it so commonly is at the start, is not characteristically predetermined in form, duration or complexity, for it is moulded throughout its course by impulses deriving from the visual exteroreceptors and proprioreceptors. It is thus profoundly unlike the motor response to electrical stimulation of the brain. It would seem therefore that we may look upon the *pyramidal system as internuncial, a common pathway by which the sensory system initiates and continuously directs, in willed movements, the activities of the nervous motor mechanisms.*"

This emphasis on the internuncial function of the cells of origin of the pyramidal tract, that is, all cells which contribute to the spinal pyramidal tract wherever they may be (and we have only a suggestion, without proof, that they are widely distributed throughout the cortex with local areas of concentration) makes necessary a search for a prior stage in the initiation and control of voluntary movement. (The mean-

ing of internuncial in the sense here implied is simply that of any connector between a receptor and an effector, not excluding several interconnectors which are totally a single functional unit.)

If the effector for our present purpose is the "lower motor neurone," the final common path to the non-nervous motor apparatus and the "upper motor neurone" pyramidal tract the internuncial, a study of the afferent neurones to the pyramidal tract will be the next appropriate consideration. It is in this study that a proper appreciation of the sensory components of movement, a function long since known but little stressed in current clinical teaching, may be appreciated. In so doing we may gain some hint as to important points of a circular track of connexions, instead of continuing to picture unnaturally a number of functions subserved by parallel tracks running in opposite directions.

In 1895 Sherrington and Mott (1895) referred to the observations of Claude Bernard in experiments on frogs and puppies showing impairment of movement undergone by a limb rendered insensitive by section of the sensory roots of its spinal nerves. Under the title "Effects of Section of whole series of sensory roots belonging to the limb" (in the ape), they say: "From the time of performance of the section onwards as long as the animal may be kept, the movements of the hand and foot are practically abolished. The defect in mobility increases from the attached base to the free apex of the limb, so that, for instance, while comparatively slight at the hip it is successively greater at the knee and ankle and greatest (amounting as regards volition to absolute loss) in the digits. In this respect it curiously closely simulates the impairment of mobility ensuing upon ablation of the limb region of the cortex cerebri, but it is in the monkey, somewhat *more severe* than the impairment following cortical ablation."

This last sentence states facts so remarkable that it is almost impossible to understand how they have so long remained almost unconsidered.

Much material for opportunity for studying sensory and motor relationships is ready to hand in the normal as well as in the diseased human being. It is best, whenever suitable cases are available, for human subjects to be used, for they alone can report intelligently and discuss understandably what subjective phenomena occur during objective actions. "Knowing" and "feeling" are difficult enough to define and analyse in ourselves. Human epistemology is a matter of indifference to apes, frogs and octopi. Sherrington says of canine experimentation (1906): "We are, of course, hopelessly cut off from introspective help." It will be with feeling that we shall be largely concerned, for sensory symptoms are so commonly a complaint of patients with dysfunction in voluntary movement. "My hand feels funny when I try and move it." Indeed, it was the observation, during routine questioning of a large number of unselected cases, that the natural use of the words "feel," "seems," "numb," "clumsy," "heavy," "helpless," "stiff," was made

to describe what turned out to be motor dysfunction, which suggested this present subject for elaboration. Clinical neurologists in an attempt at accurate analysis of symptoms are apt to insist "either it is numb *or* it is weak," but weakness is a subjective sensory phenomenon, either for the patient or observer, or both. For any change from the habitual balance of voluntary movement will be detected only by the senses.

The laboratory animal, though capable of graceful perfection in its everyday movements, does not use that wide range especially of digital skill which is commonplace for human subjects and cannot report the results of introspection. Russell (1941) in discussing the experimental psychology of learning in animals says: "We cannot observe whether an animal *feels* satisfaction or *feels* discomfort; we can only observe that it behaves in ways that we have become accustomed to interpret as signs of these feelings."

II. Origin of Movement

Movement is based on muscular activity, voluntary movement upon muscular activity in association with volitional nervous control. In voluntary movement the muscular system is the tool of the nervous system.

The precursors of the voluntary muscles are seen in the somites of the embryo within the first month after fertilization. By the eighth week of intra-uterine life the pronator teres and flexor sublimis digitorum can be made out as definite structures. They contract feebly and twitch, in the absence of nervous impulses.

The most primitive neurones are those of the spinal cord which form the spino-muscular lower motor neurone paths. They develop before the sensory fibres of the same regions. Higher motor neurones also develop earlier than high sensory neurones. Conel (1939) in a most detailed survey gives four main criteria for estimating the degree of development of the cells in different cortical areas, one of which is the degree of myelination of the areas, and states that at birth "in respect of all these criteria area precentralis giganto-pyramidalis (FA 7) has progressed in differentiation beyond any other area of the cortex. . . . The corresponding sensory areas PB and PC closely follow."

As far as lower motor neurones are concerned, according to Spiedel (1940) who took fast motion cinematograph pictures of developing neuroblasts, the mitosis of myoblasts causes agitation in the region of the nerve sprouts. His records show that a previously quiescent nerve fibre then puts out a branch to the dividing myoblast.

It appears that the primitive sequence is muscle, motor fibre, sensory fibre. Haphazard motor activity precedes its perception by sensation. The motor activity has no significance to the organism except inasmuch as it is known by sensation. In the words of Bertrand Russell (1941): "We can only remember what has been a sensible experience."

There is nothing known without the use of afferent stimuli. This

proposition as applied to the senses of smell, sight, taste, hearing, pain, temperature and touch is self-evident. In seeing we see, in hearing we hear. If we put our hand upon a red-hot piece of metal every one of these senses except taste will at once inform us of what has happened. Even taste might be used as a cross reference were it necessary. Without the senses the burning would be undetected and without response. The patient with syringomyelia relies on his eyes to prevent burns. Not uncommonly such a patient says that he did not know he was burned by his cigarette-end until he saw the blisters. The different processes all end in a state of knowledge under everyday circumstances and deliberate use such as looking at an object when requested to do so. "That is blue." "How do you know?" "I can see it." Similar is it for hearing. "That is 'God Save the King'." "How do you know?" "I can hear it." So also may we speak of smell, taste, pain, temperature and touch with all the discriminatory refinements that their integration provides.

When voluntary movement is considered from this standpoint it is at first less obvious, but nevertheless clear, that we can know we have moved only by contemporaneous afferents. The adjective "afferent" is used substantively, for the sake of brevity to mean such sensory stimuli as are provided by the sense organ or organs under discussion. These afferent elements are normally numerous and diverse in character. There is, in Brouwer's phrase, "a functional luxury". The main bulk of the afferents is "subconscious" or received consciously so habitually as to be disregarded unless attention (itself a sensory concept) be called to it. Some of them are, of course, bound up in the cerebellar mechanism, especially those concerned with equilibration, but their consideration is not an essential part of the present subject. Most of the afferents from voluntary movement are derived from sensory endings in muscle spindles and joints, and in this connexion it is an interesting speculation to consider if their functional importance may be in some way connected with the exceptionally long bursts of impulses derived from spindle fibres revealed by Adrian (1934).

Information of importance is derived also from cutaneous sensibility and the sense of sight. Less important in general use, but invaluable in restricted circumstances, are the afferents from hearing, taste and "taste at a distance," i.e. smell.

Bartlett (1947) in discussing matters of skill says: "It is certainly the case that most of our everyday actions seem to be more or less accurately graded in amount, direction, duration and other respects in agreement with corresponding variations in the stimuli required to produce them. And such graded action, however simple it may be, has at least one of the fundamental marks of skill—an effector response is not merely set off by a receptor function but is guided and determined by it. The receptor functions that are important in the case of skilled behaviour, however, are, I think, never those alone which indicate

changes in shape or volume of muscle. *They are always of that kind which claims to register something that is going on in the outside world.* So they come to be particularly identified with the operation of the special senses, and especially of those distance receptors which are the basis of the tremendous development of the central nervous system. Skill, then, whether bodily or mental, has from the beginning this character of being in touch with demands from the outside world."

The normal human being develops at a very early age, often "before he can remember," a beautifully integrated use of all relevant stimuli in any action, so that each sense performs, as if a safety device, a simultaneous check on the activity of the other receptor systems. The child sees his drum, beats it, feels the impact and hears the din, sight, sense of position, pressure, and vibration confirming the effects each of the other. The piano tuner checks the degree of rotation of the instrument he uses to tighten or slacken the strings by his ear. Countless other examples are ready to hand in everyday life.

These automatic corroborative afferents are by no means always available, nor are what we may term the primary or most important afferents. Function, in the absence of these, is impaired but not abolished. The blind and deaf know what they are doing, more or less; so does the patient with a peripheral nervous lesion or a disorder of the posterior columns of the spinal cord. But they do so *by deduction from the afferents that remain*. The blind know their eyes have moved, not by the change of scene recorded as primary sensations of their eyes, but by the afferents of the ocular muscles and orbital contents. A blind man's progress in the street depends on his ears and on his tapping stick that projects his body image in tactual form beyond his reach. Some blind people claim that they feel in the skin the "echo" of an obstacle. Caiger and Guest (1949) quote a deaf-blind man who states that for him an unexpected contact is "a sound like the banging of a heavy door and I can see a flash of light." Another blind from birth said that scarlet was the colour of trumpet music. Taste may check smell. Both seeing and blind will reject soot for food, the former by sight, the latter less well but accurately enough, cannot by taste, when sight could not be applied.

Not infrequent are the heroic examples of difficulties overcome by roundabout afferent routes. There is a photograph of an unnamed Italian boy of 11, blinded and with both arms amputated as a result of war injuries. He is reading Braille with the tip of his nose (fig. 3).

The defects produced by loss of more than one of these cross-checks is greater than the sum of the two and often totally incapacitating. The deaf furnish an example. Grades of hearing defect, in duration and degree, are clinically common.

(1) Those who become deaf late in life speak well in general, but often are noted to be talking too loud. They lack the aural check in

FIG. 3.—Photograph of blind armless boy reading Braille with the tip of his nose. (By kind permission of Magnum Photographs.)

bone and air conduction, for they may be considered to have learned the other afferent stimuli and retained them. The blind-deaf man mentioned above who was remarkable for his natural tone of speech stated that he had "some idea of control of pitch and volume by the feel of my throat."

(2) The deaf from birth can be taught speech of a sort but it is lacking in normal tonal quality and inflection. A more important fact is that the ideas expressed by such people are often childish and undeveloped in a way to suggest a correlation with the incapacity to obtain degrees of learning restraint and polish such as auditory afferents encourage. For example, a middle-aged Englishman who was a deaf-mute, had lived all his life in Great Britain but had been taught to speak by a German speech therapist. He was a selfish corpulent individual who was exceedingly boastful. He was fond of swimming and of diving especially. As a diver he was awkward and spectacularly unsuccessful, yet his habit was to stand on the end of the diving board, saying with misplaced emphasis and a German accent: "I very goot divah." Could he have heard the bystanders' comments on his subsequent entry into the water, his performance and self-criticism would have been correctly adjusted.

(3) The deaf-blind do not learn to speak unless they have learned to do so before their afflictions struck them.

These examples, chosen from a multitude of common happenings out of which the reader will be able to choose his own, serve only to show that voluntary movement as earlier stated, is ever checked, guided and polished at all functional levels by afferent stimuli. But in each case also these examples give an indication of the origin of production of voluntary movement.

III. Origin of Voluntary Movement

It may be agreed from the above considerations that the afferents of voluntary movement are essential for precise and "skilled" results. One is taught along the lines already described that voluntary movement as it proceeds is checked by the afferents. This teaching, however, implies that voluntary movement is something started elsewhere, something apart from afferent checks, something which is polished by afferent checks; in fact, something. Arising erroneously as the next step from the conception are the "patterns of voluntary movement" (Wright, 1945) and all the picturesque "keyboard" and "switchboard" arrangements set going by "volition"—the idea that "repetition sets up a potential in effector mechanisms" which "will" has but to choose from and fire off. To correct our direction in these false and nebulous abstractions an analogy may be helpful. When one uses the automatic telephone, the dialling of a number has its appropriate effect and results in the production of distant phenomena. But not even a layman would suggest that the telephone is responsible for selecting the number and requiring it purposefully at the appropriate moment. The motor apparatus is to voluntary movement as the telephone is to the conversation.

If we do not think thus we are dependent upon that grotesque homunculus (fig. 4) with huge lips and thumbs, upside down in a hatched and dotted textbook brain pulling switches in the motor cortex. When this has been done the sensory apparatus, including the cerebellar mechanisms, has to steer as best it may the otherwise flailing action of muscles and joints.

How does voluntary movement come about if not thus? Let us consider early voluntary activities, choosing for examples the acquisition of (1) speech, (2) the use of a spoon, in a baby, and (3) the learning of a new skill such as piano playing in an adult. The processes are similar in principle.

(1) *Acquisition of speech.*—Speech function starts as a chance occurrence in the infant as expiration (sometimes inspiration) with the larynx set in a particular position. Under these coincidental conditions of quite mechanical quality a sound is produced. As time goes by the production of crude sound, sometimes varied by closure of the lips, or movement of the tongue, resulting in the age-old first and gratifying "words" "Ma-Ma," "Da-Da," is seen by the child, or felt, from food or general attention to produce occasional effect. Arnold Gesell (1946),

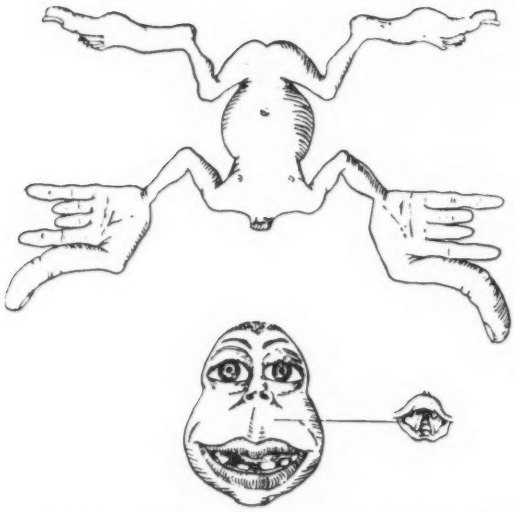

FIG. 4.—Part of diagram by Penfield and Boldrey. Sensory and motor homunculus. Visualization of the order and comparative size of the parts of the body as they appear from above down upon the Rolandic cortex. (*Brain*, **60**, 1937.)

who has made such a detailed study of behaviour in premature and normal babies, states in his popular exposition : "In the first month the baby makes small throaty sounds. At 16 weeks he 'talks' to himself. At about 32 weeks he utters syllables like 'Da.' *He can imitate only those sounds which he has already made in his babbling sound play.*" He also hears noises which he can gradually imitate by adjustment of his vocal apparatus *in known positions* and by intelligent elaboration of these processes the child makes, eventually, a sensible voluntary response in speech. In the preceding sentence the word *"known"* is the vital one. The positions are known by the afferents supplied from the mouth, throat, larynx, diaphragm and respiratory muscles. The correctness and effectiveness are checked by sight, hearing and the supply of warmth, food or contact. *The efferent process, the voluntary movement of speech develops secondarily to the prior afferents.*

We may test this for ourselves by "speaking without actually doing so." We find that we can tell at once which essential is lacking. It may be articulation, or supply of wind to cause laryngeal sound, which is missing. We *can* tell at once which is lacking by the awareness of the mechanism not used, and one's attention is focused, to the exclusion of the normally operating components, upon it.

(2) *The voluntary movement of getting a spoon to the mouth.*—This begins in haphazard and useless movements, which, as the weeks pass by, are observed by the eyes, and probably checked by the muscle and

joint afferents so that a selection and refinement of control is effected. Gesell's photographs (1945) show that at 16 weeks a child stares at a block on a table. At 24 weeks he reaches for the block *at sight*. Later comes the day when the child can direct the spoon to the region of the mouth, and soon the motions of eating voluntarily and unaided are neatly done. The niceties of spoon manipulation with pronation and supination adjusted to ensure clean entry to the mouth are in part excited by tactile afferents from the chin and face, with added auditory encouragement and visual example of older people.

(3) *Acquisition of specialized skilled voluntary movement—keyboard playing*.—The initial process in playing a keyboard instrument (a skill, especially in organ-playing, needing the highest degree of precise rapid variable movement of willed type) is imitation. One watches one's teacher who depresses a key or one dabs about from note to note until one's auditory impulses agree with the sound already in being. When the understanding of written music is obtained, the player, from a series of more or less black dots seen on his music paper, plays appropriate combinations of varying complexity. From simple visual stimuli of this type, semibreves, minims and so on, not only the type of voluntary movement is able to be determined but also the duration, absolutely and relatively, with appropriate consideration of the circumstances. It is a digression but an interesting one, perhaps, to consider how varied and yet more complex are the stimuli of everyday life compared with a sheet of music. The responses to general visual stimuli are more complex and more diverse, yet are of the same order as those of the organist. Multiplication of all the afferent stimuli of our daily life, graded and of kaleidoscopic profusion, is only a still more complex arrangement of the same type. It may be that response of everyday voluntary movement is the inevitable result of these stimuli. A black dot on a piece of paper is responsible for initiation, maintenance and cessation of a voluntary movement, and will have relative values within the whole structure of the special skilled performance. Its value and meaning will vary from day to day and from person to person, yet a constant pattern is perceptible. A similar pattern is perceptible in behaviour, and the variety is only a factorial product of the stimuli of daily existence.

To return to the musician, by this process of effecting as voluntary movement the stimuli from his senses, he develops and increases his skilled performance. But he is not learning "patterns of voluntary movement" as we are so often told. He is learning *patterns of sensation. This is a fundamental point.*

The player is learning sensation not movement. He cannot learn movement. He can only learn the "sensations" which accompany movement. Bartlett (1947) says: "The common belief that 'practice makes perfect' is not true. It is practice *the results of which are known* that makes perfect." He can but see how his fingers have moved, hear the sounds produced and feel the motions of his digits, wrists and

forearms. We have only to think carefully about whatever skills we may possess and our performance of them to find that we are learning sensation, not movement.

The fingers-thumb test will serve as a standard example for this purpose and is carried out as follows: The performer has to oppose the thumb of one hand to each finger of the same hand, starting with the little finger and ending with the index. The movements are repeated as long as required and may be done fast or slowly, the faster speed needing greater skill and correspondingly being earlier impaired as soon as normal performance is lost. The test involves movements of both opposed digits and is not in any way a "discrete" movement of one digit to another which is still.

When we watch our friends or patients doing this we see that they first raise the hand to the most convenient position for sight, this commonly being at the centre of their visual field at a distance of 1-2 feet from the eyes. With varying degrees of skill they "run off" the movements. If one does this test oneself, it is only after an effort that one closes one's eyes before starting. If it is done with the eyes closed one still has a visual image running concurrently with the felt emotions. Though this image is not what we call "sight" yet we stare at it as we do the fingers when the eyes are open. As one repeats the test over and over again with the eyes closed, 4.3.2.1., 4.3.2.1., 4.3.2.1., one feels, as one thinks about it, a great sensation of the whole affair, a clear intense and even exciting awareness of the moving parts, and especially of the areas of skin at the fingertips as they come in contact with each other. If one stops at this point for a moment before restarting one feels that the fingers and thumb are sending strong afferents of their position. If one now opens one's eyes one is usually staring at the digits, enhancing their excitatory state. (It is occasionally found, especially if the patient is attending carefully to his examiner, that his gaze is fixed on the examiner's face when he opens his eyes, in a search for afferents of approval or instruction.) From the digits the movements start again.

The other hand has remained ignored, and quite still.

What will break into this rhythm of sensation? Other sensations of sight and sound and touch, the burst of pain in trigeminal neuralgia, the sight of a crowd of students, the sound of the clock, the smell of lunch. Those who play the piano will readily admit that once a piece is learnt, breakdown comes from sensation. It may be a sudden awareness of the black-spots of the musical notation. It may be the sight or sound of the approach of a critical friend. It is often the *awareness* of the hands in a hitherto smooth and unaugmented series of learnt afferents, "educated skill," which causes the collapse of voluntary movement. Bartlett says: "One of the very common features of diminishing skill is an increased awareness of what the whole body is doing." By an effort of "forgetting" and "thinking of something

else" one may sometimes avoid the unbalancing new afferents before it is too late.

Adrian (1934) notes a comparable phenomenon as follows: "If our attention is focused on a mobile and sensitive part like the hand it is not at all easy to keep all the muscles completely relaxed when the sensitiveness of the skin is tested. Unless we take pains not to do so, we make slight movements, and these keep alive the sensations from the rapidly adapting end organs."

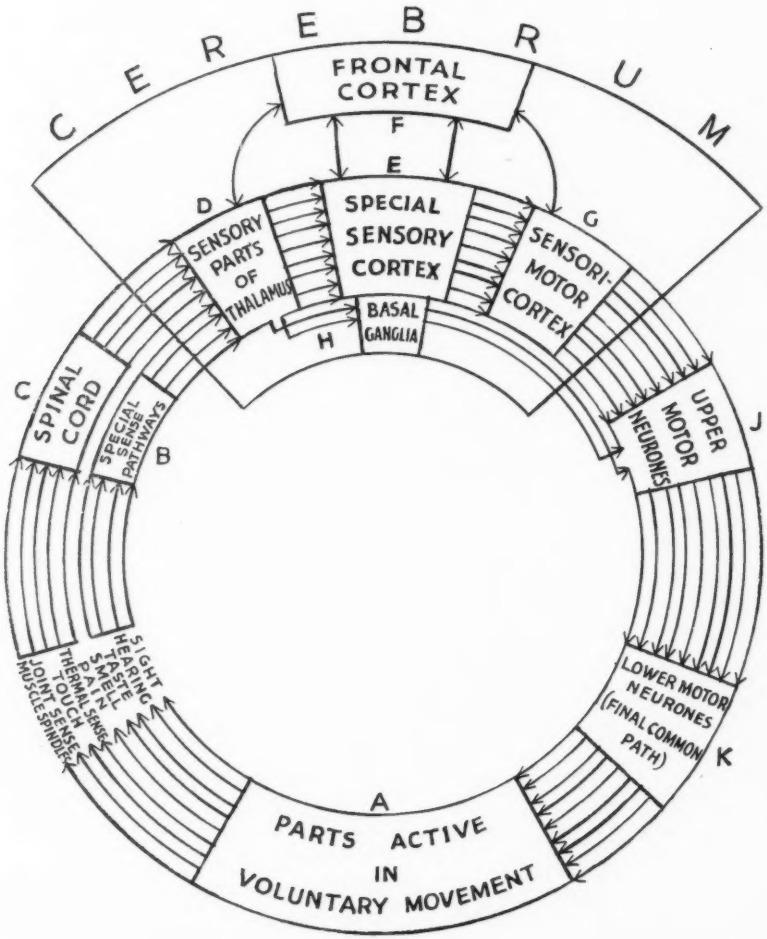

FIG. 5.—Sensorimotor scheme of voluntary movement. For key to letters *see* text.

At this point it is suggested that :

(i) *In voluntary movement, sensation and motion form a single indivisible continuous process.*

(ii) In the development of voluntary movement it is the peripheral motor mechanism which "teaches" the central apparatus. The motor cortex reproduces voluntarily what has already been done involuntarily. *It follows inevitably that in daily life the motor cortex deals in movements, for it is taught by the receptors only movements.*

(iii) These ideas may be illustrated by diagram (fig. 5) which is not intended as an anatomical scheme. The parts active in voluntary movement (A) give rise to sensory stimuli (the basic information with "cross checks") which pass via the special sense pathways (B) or the spinal cord (C), either direct in special tracts such as the visual, or in contiguity with other forms, an arrangement we find in the fillets of the brain-stem, to the sensory portions of the thalamus (D). These are further relayed to their several sensory cortical areas (E) and thence to the sensorimotor cortex (G) (which may be a much larger region than at present generally accepted). There are interconnections between (D), (E), (G) with the frontal areas (F). The thalamostriate pathways (H) connect the thalamus to the basal ganglia. From the pyramidal and extrapyramidal areas of origin, impulses pass down the brain-stem and spinal cord as "upper motor neurones" (J) and so via "lower motor neurones" (K) to the "parts active in voluntary movement" (A) once more.

IV. Clinical Aspects of Voluntary Movement

There follow some descriptions from clinical cases which may illustrate disorders of voluntary movement arising from lesions anywhere on the sensorimotor circle.

For the sake of brevity, only the sensory disorders of voluntary movement will be described in detail, for muscle disorders and lower motor neurone diseases are well recognized and relatively simple to understand.

(1*a*) *Lower Motor Neurone*	*Interior Poliomyelitis*, and its effects.
(*b*) *Lower Motor Neurone*	*Progressive Muscular Atrophy.*
(2) *Upper Motor Neurone* (Cortico-spinal or "Pyramidal")	*Primary Lateral Sclerosis* variety of *motor neurone disease* or combination of (1*b*) with lateral sclerosis.
(3) *Upper Motor Neurone* ("Extra-Pyramidal")	*Paralysis agitans.* *Hemiballismus.*
(4) *Upper Motor Neurone* (Prefrontal)	*Leucotomy.*
(5) *Sensorimotor Area*	*Cerebral vascular disease.* (Illustrations by 2 case records).
(6) *Upper Sensory Neurone* (ii) *Parietal*	

(7)	*Upper Sensory Neurone* (i) (*Thalamo-cortical*)	
	(*a*) Visual, Auditory, Gustatory, Olfactory	Local lesions.
	(*b*) "Common sensation."	As in (5)
(8)	*Lower Sensory Neurone* (iii) Auditory fillets, Dorsal nuclei } to thalamus	*Brain-stem lesions of fillets.* (Dr. Martin's case)
(9)	*Lower Sensory Neurone* (ii) (Second common sensory neurone in spinal cord)	*Tabes dorsalis.* *Disseminated Sclerosis.*
(10)	*Lower Sensory Neurone* (i) (Primary neurone from organ to spinal cord)	*Experimental posterior root section.* *Phantom Limbs.*

(1) *Disorders of lower motor neurones.*—The part is deprived by reason of necrosis or atrophy of its simplest motor innervation. Muscles and movements are paralysed in varying degree. The parts affected are reported as "heavy," "clumsy," "weak," "useless."

(2) *Disorders of upper motor neurones ("pyramidal").*—In these disorders, weakness of individual muscles is demonstrable by formal testing, but main symptoms are derived from disorder of movement. They are described in terms all of which are perceptual. Such words as "helpless," "drags," "queer," are used. Weakness is recognized and intelligent efforts at circumvention will be frequently found. It is reported from a spinal injuries centre that if only 10 major muscles are remaining in use, the patient can be taught to walk.

(3) *Disorders of upper motor neurones ("extra-pyramidal").*—Stiffness of willed movement and impediment by unwished involuntary movements characterize these disorders. One of the most striking and almost invariable complaints of patients with extra-pyramidal involuntary movements is: "The shaking is worse when I am upset or people look at me." They say: "It has been worse since I knew I had to come up to hospital. It isn't nearly as bad as this usually, but your looking at me somehow makes it worse." Attention and knowledge from their eyes and ears accentuates their defect and of course sight and hearing are purely sensory stimuli. As one would expect, the involuntary movements often cease during sleep, only to recur as soon as the patient has roused to full awareness. In that half-consciousness between sleep and waking the movements are absent.

Recent work on normal skilled movements suggests that such movements are in fact discontinuous, at a fast rate of repetition, and there may be some connexion between the discontinuity of involuntary movements (which may decrease or disappear as voluntary movement of the affected part is increased) and the discontinuity of normal voluntary movement.

In (1), (2) and (3), voluntary movement as demonstrated by the fingers-thumb test is impaired.

(4) *The frontal cortex.*—Lesions are seen chiefly as the results of tumour formation, vascular disease and surgery in the treatment of psychiatric disorders. Ablation experiments in animals have also been carried out in an attempt at more accurate localization of lesions. Thalamocortical projections of the frontal cortex are widespread (cf. fig. 3). Patients suffer from a lack of spontaneity of voluntary movement and when both the frontal lobes are involved there may be total loss of all volitional activity. The patient lies motionless in bed, helpless and incontinent, yet able to perform simple actions to command and hold a sensible conversation. A defect of recent memory and "all behaviour adaptation dependent upon this disability" are found. These hamper the execution of voluntary movement. The specific defects of voluntary movement in the chimpanzee with a unilateral "premotor" ablation are described by Jacobsen (1932) as follows: "Although premotor lesions did not result in residual motor deficits which made the execution of fine adaptive movements difficult, the organization of these movements, as patterns of response . . . was greatly disturbed and necessitated post-operative relearning." Fulton (1946) emphasizes the failure of organization of movements in the patterns of response even when of a very simple character and any such deficit needed a longer period of retraining. The fingers-thumb test is poorly executed owing to the indifference and memory defect of the patient.

(5) *Disorders arising in the sensorimotor cortex.*—Details of a man suffering from cerebral vascular disease affecting the central region of the hemisphere are given to illustrate a defect of voluntary movement from a *cortical sensory* lesion.

Case Record 1.—A man aged 63 was referred to Mr. Harvey Jackson for consultation at The National Hospital, Queen Square, in May 1948. He had been for many years a skipper of small craft in the Mediterranean Sea and inland waterways of France, leading a vigorous life without ill-health. He complained of headaches and jerking attacks involving the left side of his body. These symptoms had troubled him for three years. The first fit occurred soon after rising in March 1946. He stretched both arms out sideways and then found that the left one was rigid so that he could only with difficulty, and the use of his right hand, get it down to his side. The left arm twitched a few times and then was normal again. He "felt funny generally" but went to work as usual. That day he consulted "a quack friend," and while in his house straining somewhat to pass water his left leg suddenly gave way and he fell. He was able to move the leg clumsily and managed with assistance to get home by car. That night he had persistent jerking of the left arm and leg, each bout being preceded by a feeling of the left eye becoming "heavy" and the left side of the face "screwed up." The jerking movements consisted of involuntary flexion of the elbow and hip.

In the summer of 1946, after a further brief spell of similar symptoms, he lost consciousness and was admitted to a hospital where, as he improved enough to be examined, he was found to have a quadrantic homonymous hemianopia "of transient duration." He was also noted to have "motor and sensory defects of a cortical pattern on the left side with astereognosis and tactile inattention. All investigations were negative and his condition was thought to be due to cerebral vascular disease."

Early in 1948 he was admitted to hospital, again unconscious. When well enough to co-operate, he showed a left homonymous hemianopia and a central type

of left facial weakness. The left arm showed weakness and there was "impaired sensation in the left arm and leg." The left plantar response was extensor.

The spinal fluid was under 220 mm. pressure but was otherwise normal. The Wassermann reaction was negative in blood and C.S.F.

He made a gradual improvement and left hospital, to lead a quiet life in the suburbs of London. He came to the National Hospital for final advice before setting off for the Hebrides, where he "hoped to be able to potter about among small boats again."

Examination.—He was a pale, heavily built man whose blood pressure was 240/120 mm. of mercury. He walked slowly and breathlessly but with no obvious local disorder of gait. His visual acuity was 6/6 in each eye and confrontation tests showed full fields. The visual fields were charted by perimetry on the Bjerrum screen and no defect could be made out with 2/330, 5/330 and 3/2,000 white objects (in spite of his former hemianopia). The fundi showed normal optic discs, some arteriosclerotic change in the retinal arteries but no hæmorrhage or exudate. Ocular movement and pupillary reactions were normal. There was a slight "central" facial weakness on the left side. The speech was moderately slurred and indistinct.

The right half of the body was normal.

The left arm and leg showed normal resistance to passive flexion. Power and nutrition of the skin and muscles were normal.

Voluntary movement of the left hand was tested in detail. The fingers-thumb test and shoelace tying were used to assess fine movement co-ordination. The patient said: "That hand (the left) is not too bad as long as I can see it. I can do buttons up in front but not at the back. I need my eyes to guide me. I can only do up my collar if I use a mirror." With his eyes open he was less facile with his left hand than the right in doing the fingers-thumb test and he was slow in tying his shoelace in a bow. He did manage to oppose his digits and thumb in succession, rather clumsily, slowly and with apparent efforts and discomfort. He could tie a good half-hitch and bow on each shoe.

With his eyes closed his performance was altogether different. His attempts at the fingers-thumb test took the form of variable purposeless waggling of the fingers, to and fro and sideways, with occasional flexion and extension of the distal two phalanges of all the fingers, the proximal ones being extended all the time. He succeeded in making a half-hitch on his shoelaces using his right hand only. He tried to use his left hand to form a bow but could not arrange his fingers and thumb in any suitable position to grasp or let go at the correct moment. He attempted to adjust the left digits with his right hand but as soon as the left was on its own it fell into a helpless half-open posture.

Vision was essential for him to fasten his collar and tie his tie.

In testing the left leg, the heel-shin test was rather less well performed than normally, with eyes open. With eyes closed, the movements were very clumsily carried out. As he moved his heel up and down his right shin, his left arm and hand were seen to flex and extend

comparably. He said "this arm *will* move. I can't stop it except by holding it." There was no movement of the right arm on moving the left, nor on exerting the left arm or hand in any way: nor did any exertion of the right limbs cause any left-sided movement.

The reflexes were all brisk. The tendon-jerks in the left arm were a shade brisker than in the right. The abdominal responses were equal, as were the knee and ankle jerks. The right plantar response was always flexor. The left was sometimes flexor and less frequently equivocal. It was less frequently still (3 times in 20) extensor.

Sensory testing, as would be expected, showed wherein the origin of his disabilities chiefly lay. The right side of the body was normal throughout. On the left side light touch tested with cotton-wool and light finger contacts was generally normal. Pin-prick was appreciated as well on the left side as on the right. Cold tap water in a test tube seemed colder on the left hand and forearm than it did on the right, but warm and hot water felt the same as on the right.

Vibration sense was unaffected.

Joint position sense was grossly affected on the left. The outstretched left arm could be displaced slowly through 90 degrees without detection and the patient could not imitate a set posture of the right elbow and fingers. Position sense of the elbow and wrist was severely impaired and appreciation of position of the digits quite lost. There were occasional inaccuracies in judging ankle position, and many in toe position. The defects in the left leg were less than those in the left arm and hand.

Two-point testing showed inability to discriminate one from two at 5 cm. on the left hand and at 10 cm. on the left foot and shin. He could not judge 6 in. digits written on the left forearm or shin, though he did this with accuracy on the right side.

Appreciation of solid form was tested with his own jointed metal shirt armband. He called it "maybe a small coin" and with his eyes closed failed to handle the object at all. He recognized the object readily in the other hand or with his eyes open.

The patient had had a gross lesion of his right cerebral hemisphere at about the central region. From this he had made a good recovery, especially as far as "motor area" and optic pathways were concerned. He was, however, left with *a marked sensory loss of cortical or subcortical type*, which, though moderate in its effects for simple purposive voluntary movement under ocular guidance, *was severe enough almost to cause total paralysis when he was unable to use his eyes.*

(6) *Disorders arising in the parietal lobe.*—We are here faced by the most complex disorders of sensation and movement. They are the most "malignant" and tantalizing in that they are caused by obstacles of sensory interpretation, which bar to a normally constituted lower and peripheral motor apparatus the drive of praxis and gnosis. The disability for voluntary movement from this sensory disorganization is

profound. It may be masked by symptoms or signs of associated cerebral disease, as is shown in the case record which follows below, but the basic fact of cessation of voluntary movement is clear. The responsible lesions are not, however, motor but sensory. Apraxia is only a special term for what is not more than "high level" sensory ataxia, in spite of the definition by Kinnier Wilson that apraxia is: "A disorder of cerebral function characterized by inability to perform certain familiar purposive movements, in the absence of motor and sensory paralysis and ataxia." The "sensory paralysis and ataxia" of his definition are those comparatively low sensory mechanisms which precede eupraxic and eugnostic integrations. Dyspraxia is itself a form of paralysis, at a level where it is hard to disentangle the sensory and motor elements. In testing for dyspraxia we are testing sensory neurones higher than the simple ones we are familiar with—those which lead up to "cortical" sensory appreciation.

By the time a patient is sufficiently ill to come under specialized observation his lesion is usually a gross one, and it impinges upon fibres dealing with a large number of sensations. Such a lesion may disorganize visual relays to and from the occipital area, auditory relays from the temporal region. Proprioceptive and other exteroreceptive afferents will be destroyed at their termination or in their relays from the thalamus.

These lesions will therefore provide an inconstant protean clinical pattern of disorder for which sets of tests can be endlessly elaborated. Clinical neurologists have been fascinated by this problem which has an elegant, mysterious abstruseness. Eponymous syndromes and neological signs have been created in an attempt to analyse disorders and localize function to such an extent that now the student may with credit reel off a list of terms which he believes are localized functions of particular gyri, without considering how artificial or disintegrated are his ideas.

The more rigid our localization of function, the more limited is our capability of understanding.—For example, "finger agnosia" is a special feature in "Gerstmann's syndrome," associated with lesions of the left angular gyrus, and one could therefore dot upon a schematic brain "a centre for finger gnosis." Spillane (1942) tells us "Gerstmann's syndrome may appear at any time during the course of an illness produced by a lesion, vascular or neoplastic, in the parieto-occipital region." Fulton (1946), however, points out: "It is almost certainly a manifestation of intellectual deficit. . . ." "Finger agnosia may be seen in frontal lesions. The total inability to recognize, indicate on command, name or choose the individual fingers or the patients' own hands or the hands of others depends on total cerebral integration." Yet, paradoxically, Fulton states: "Topography[1] rather than function

[1]Topography is defined in The Concise Oxford Dictionary (1931) page 1294, as "Detailed description, representation on map, etc."

is often the determinant of the structural organization of the nervous system."

It is by no means certain that anything like a constant pattern of anatomical or physiological function exists. The simple study of a few fixed brains will show how hard it is to identify corresponding gyri and sulci in specimens. After the initial surprise and exasperation comes the reflection that we at present need the idea of a stereotyped brain with unvarying habits for clinical interpretation in face of the facts of variability and individuality.

We know of "aural memory" and "visual memory," the "good ear" and "keen eye" in the normal person. We hear of the refined hearing and touch of the blind, of the skill in visual interpretation of the deaf who lipread with skill and accuracy. It must be clear that their sensory integrations differ, that anatomical lesions will produce different psychological results. In the blind armless boy who reads with the tip of his nose and lips, where would a lesion be that produces alexia?

Case Record II.—A woman (M. R.) of 53 was admitted to the National Hospital, Queen Square, under the care of Dr. Macdonald Critchley in November 1948. She was incapable of giving any account of herself. Her husband said that she had been having "attacks of coma" for three months. Her family history was normal and her past health had been exceptionally good.

Three months before admission she had collapsed suddenly and was unconscious for a short period. On coming round she appeared dazed, but could recognize her husband. She moved her legs, from side to side, in a rhythmic manner for about eight hours. She then fell asleep, and when she awoke she appeared her normal self again.

Two months before admission she had a second attack while shopping. She appeared confused and spoke strangely. She had to be helped home and seemed unaware of her surroundings. After sleep she once more appeared normal to her relations.

Two further attacks of generally similar pattern took place in the succeeding few weeks.

Four days before admission, she failed to wake at the alarm clock's ring, and her husband could not rouse her. Half an hour later the rhythmic leg movements began but she was unable to talk and it was impossible to attract her attention. She soon fell asleep and remained so for thirty-six hours. She could not be roused during this time and was incontinent. She awoke and appeared normal for about two hours. She then fell into a motionless speechless state. At this point she was transferred to the National Hospital.

On admission she was found to be wasted and dehydrated. She lay in bed with her eyes open. She breathed and blinked normally, but was unresponsive to her surroundings. She did, however, grimace to painful stimuli. She could suck and swallow. *She made no voluntary movement whatsoever.* The only limb movements noted were in response to stroking the soles of her feet.

Skiagrams of the skull and cervical spine were normal. The sense of smell was not tested. Ophthalmoscopic examination of the ocular fundi was negative. The pupils were equal, central and circular, and reacted sluggishly to light. There was no spontaneous movement of the eyes which gazed at the ceiling. When her head was rotated it was noted that the eyes moved equally and fully in all directions. There was no nystagmus. The corneal reflexes were brisk and she grimaced at pin-pricks on the face. The facial movements in response to pin-prick were sym-

metrical. Auditory and vestibular functions of the eighth nerve could not be assessed satisfactorily. Sensation on the posterior pharyngeal wall was normal, and the palate rose in the mid-line. The eleventh and twelfth nerves could not positively be tested but there was no abnormality of the sternomastoids, upper parts of the trapezii, or tongue at rest. Gait and stance could not be tested. Tone as tested by passive flexion and extension of the elbows and wrists in her upper limbs was reduced. Tests of power and posture maintenance could not be carried out, as she remained motionless. Routine tests of co-ordination were not able to be done.

Apart from a somewhat greater feeling of resistance to passive movements the legs showed a similar state to that of the arms.

The tendon reflexes were symmetrical and not increased. The abdominal reflexes were absent and the plantar responses extensor.

The cardiac rhythm and size were normal. At the apex a loud systolic murmur was heard. The blood-pressure was 200/110. The peripheral vessels were moderately hard. Examination of the lungs and abdomen showed no abnormality.

The urine showed a trace of albumen, no sugar and no casts. The blood-sugar was 0·160 gramme per cent. Blood-urea on the day of admission was 176 mg. per cent falling to 46 mg. per cent by the evening of the next day. A full blood-count showed nothing unusual.

The X-rays of skull, chest and pelvis were normal.

The E.E.G. (Dr. Cobb) detected a left-sided abnormality without precise localization. It was thought that some lesion probably lay deep in the antero-central part of the hemisphere.

The C.S.F. was under 90 mm. pressure. It was clear and colourless, contained 2 cells and protein ·04 gramme per cent. The Lange curve was unchanged and the W.R. negative.

It was thought she might have a third ventricle tumour, and ventriculography was carried out by Mr. Wylie McKissock. The ventriculogram showed slight symmetrical dilatation of the lateral ventricles. The third ventricle was normal. The appearances suggested (cortical) atrophy.

She lay in a state of immobility for about a fortnight and then in a matter of one or two hours changed for the better so that she was found to turn her head and eyes towards her examiner when he said her name. To command she shut her eyes, put out her tongue, showed her teeth and moved her right arm and leg. She did not move the left arm or leg, and when asked to do so she always moved the right limbs. Although she did not move her left arm to command she always moved it back to its position of rest, flexed across the chest, if it had been displaced. She did not respond to painful stimuli on the left side of the body.

Dr. Critchley demonstrated her unawareness of objects on her left side and her unwillingness to look to the left. He suggested that she might have a bilateral softening of the brain, more right than left, causing visual and spatial disorientation and an ignoring of her own body.

Her condition gradually deteriorated. At Christmas she had a series of major epileptic convulsions. No striking changes took place in her condition and she quietly died early in February.

Extracts from the clinical summary of the registrar, Dr. Reinhold, are as follows:

"*She was generally mute,* but on rare occasions uttered a word or two. She seemed able to understand what she heard as on rare occasions when she was asked how she felt she answered "better." Painful stimuli caused her to make a withdrawal, not necessarily of the limb so stimulated but perhaps of another part, as if she could not localize the stimulus. *She lay inert in any position in which she was placed. No spontaneous movement of her limbs or trunk occurred, though she was not paralysed* as all limbs could be moved when painfully stimulated."

Post-mortem examination (Dr. Blackwood) showed bi-parietal cerebral softenings. Detailed histopathological investigations are not at present complete.

This patient showed a *complete absence of voluntary movements, from lesions involving the "sensory cortex" only.*

(7*a*) *Loss of sight, hearing, smell and taste.*—Disorders resulting from defects of these sensory modalities are similar in quality but of great variation in quantity. The blind are defective in voluntary movement from lack of spontaneity, which is in part a form of visual reflex movement. A blind patient can touch the tip of his nose or do the fingers-thumb test as well as anyone. But he cannot make more than a wild shot at, say, the tip of his examiner's finger. Nor can he touch his own nose, if he has a lesion affecting postural sensibility. His inability to touch his examiner's finger is no less a defect of voluntary movement than inability to touch his own nose if he has position sense loss in his limb. Nor does it differ from the incapacity of a patient with normal vision and postural loss who attempts the test with eyes closed. Tradition and thoughtless routine have, however, installed in us a feeling that there is a significant difference in these varying circumstances. It will be pointed out that with eyes closed, "sight doesn't come into it: the patient is using proprioception only." This is precisely the point. To illustrate the defect in execution of the fingers-thumb test, one has only to say to a blind patient "Do this" as one performs the motions and he is quite unable to see what to do. He can manage to do the movements only if he is provided with sufficient aural instruction to "get round" his blindness.

Loss of hearing, smell and taste causes defects of voluntary movement in so far as the movement is a response to hearing, smelling and tasting. A deaf man will not do the fingers-thumb test unless by watching pantomime, lip-reading or seeing written instructions his eyes enable him to "get round" his deafness.

The anosmic or ageustic patient will not be able to do his fingers-thumb test in response to a smell or taste. Such difficulties are admittedly infrequent. If, however, we consider two people, one with normal sense of smell and the other defective in it, from such a lesion as an olfactory groove meningioma or effects of head injury, and they are subjected to a lethal concentration of an odorous poison gas, their resulting behaviour will be decisive.

(7*b*) *Defects of "common sensation" of cortical type.*—The effects of such lesions have already been discussed in Section 5.

(8) *Brain-stem sensory lesions.*—A most striking and excellent example is described by Martin (1949) in his Lumleian Lectures of 1947 on "Consciousness and its Disturbances." His patient had, within a period of ten days, lesions affecting her median and lateral fillets first on one side and then on the other. Autopsy confirmed the clinical diagnosis and there was demonstrated a "hæmorrhage which had spread to involve the whole of the median fillet on each side and the adjacent lateral fillets as well as the sixth nuclei and the right facial nerve. All the anterior part of the pons, including the pyramidal bundles, was intact."

"The patient was at first drowsy; later it was 'impossible to keep her awake'. . . . She fell into a deep sleep; and, even when we raised her eyelids, she did not rouse properly, and in the course of a few days of gradually deepening coma she died."

Comatose patients are motionless. Coma, as defined by Henderson and Gillespie (1936) is "the profoundest degree of stupor; all consciousness is lost; *there is no voluntary activity of any kind.*"

We assume, therefore, from this case that *bilateral lesions of the fillets, structures unequivocally sensory in function, are accompanied by total loss of voluntary movement.*

(9) *Sensory lesions of the spinal cord.*—These are clinically fairly common, though cases of marked tabes dorsalis with locomotor ataxia are no longer easily obtainable in large numbers for observation, in the way that thirty years ago they must have been. The "useless limb" resulting from a fresh plaque of sclerosis is not always due to a purely sensory lesion. (It has not been thought satisfactory to use as an illustration any case, such as that of spinal neoplasm, in which there was any significant admixture of demonstrable "pyramidal disorder" as indicated by increased tone and tendon reflexes or extensor plantar responses. It is an acknowledged clinical finding, however, that in disseminated sclerosis voluntary motor incapacity is greatly increased by sensory deficit.

In tabes dorsalis, where the lesions so clearly involve the sensory pathways of the cord concerned with touch and especially joint position and muscle sensibility, the defects of voluntary movements may lead to complete paralysis, though motor power in the limbs may remain unimpaired to the end.

The following descriptive extracts are taken from Gowers (1892): "The characteristic inco-ordination of movement develops gradually. It is always increased (as Romberg has pointed out) by closure of the eyes, and at first may only exist when the guiding influence of vision is thus withdrawn. . . . The effect of closure of the eyes is greatest when sensation in the soles of the feet is defective, but does not depend on this loss; it may be marked when sensation on the soles of the feet is

perfect. The early defect in co-ordination may be discovered by the patient when he shuts his eyes in the process of washing the face. In a further degree of inco-ordination there is inability to stand with the feet together, even when the eyes are open, and the patient is only steady when the feet are wide apart. . . . As the defect progresses, uncertainty is felt in walking, even with full visual guidance, especially on uneven ground or on a very smooth surface. . . . The commencing defect (in the arms) is first revealed by delicate movements such as writing. When slight it may be conspicuous if the patient tries, with closed eyes, to touch some object such as his own nose. As it increases, all movements become irregular; it is impossible for the patient to button his coat or to pick up a small object from the table. . . . Occasionally, the muscles of the trunk present a similar ataxy. Thus, one patient could sit steadily on the chair when his eyes were open, but if he closed them, would at once fall off. . . . Even with extreme inco-ordination motor power may be unimpaired."

These examples furnished by cases of tabes dorsalis are more convincing than those by disseminated sclerosis, because the proportion of involvement of sensory and motor tracts is accurately known.

In both conditions treatment is traditionally directed to the curative re-education of the sensory ataxia and various forms of exercises are directed to this end. It is striking how patients with sensory ataxia fix their eyes upon the floor and remove their gaze at their peril.

(10) *Sensory lesion between the locomotor apparatus and the spinal cord.*—Peripheral nerve injuries are not considered in this heading as it is impossible to examine the function of the motor and sensory components separately by clinical methods. It might be done by the use of the differential anæsthetic properties of novocain, but the type of fibres involved could not be stated with certainty at any particular moment.

It is possible to refer again to Sherrington's (loc. cit.) experiments on posterior root section in the ape. The sensory destruction resulted in a defect such that "movements of the hand and foot are practically abolished. The defect in mobility increases from the attached base to the free apex of the limb, so that, for instance, while comparatively slight at the hip it is successively greater at the knee and ankle and greatest (amounting as regards volition to absolute loss) in the digits.

"In this respect it curiously closely simulates the impairment of mobility ensuing upon ablation of the limb region of the cortex cerebri, but it is in the monkey, somewhat more severe than the impairment following cortical ablation."

We may also consider the facts stated by Riddoch in his paper on Phantom Limbs (1941). He states: "Another important effect of postural loss in the stump is great limitation or even absence of voluntary movement of the phantom fingers while the clarity of the phantom outline may be unimpaired." Again: "Voluntary movement of painless

phantom fingers or toes is usually possible and often considerable. One of the main factors upon which it appears to depend is preservation of postural sensibility in the stump." A further important and confirmatory detail is: "Should postural sensibility later return to the stump, the phantom again comes to move with it."

These examples show strikingly the dependence for voluntary movement of a limb upon peripheral sensory mechanisms.

In this whole series 1–10 *there is no sensory lesion which does not have its appropriate effect upon voluntary movement.*

In the diagram (fig. 6) the sites of these lesions 1-10 are indicated.

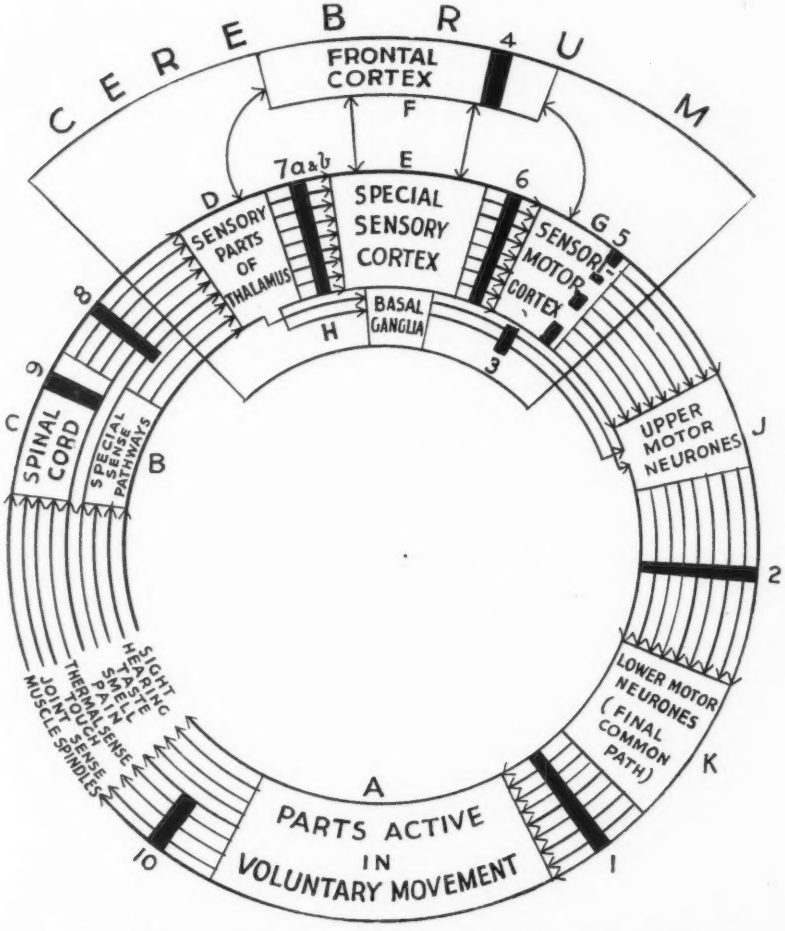

FIG. 6.—Sensorimotor scheme to voluntary movement, with clinical lesions. For key to letters and figures *see* text.

V. Summary

(1) The traditional belief in a division between motor and sensory functions is reviewed.

(2) An attempt is made to establish a closer relationship and interdependence of sensory and motor functions in the exercise of voluntary movement.

(3) The possibility of a less precise scheme of cerebral localization is suggested and a plea made for a more integrated and physiological approach to clinical localization.

(4) A scheme for considering normal sensory and motor functions as a continuous proceeding is represented diagrammatically. The dependence of the brain upon the peripheral sensory mechanisms for learning is especially emphasized.

(5) The site and effect of lesions of the central nervous system are considered with especial reference to the preceding theoretical considerations.

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HEREDITARY ATAXIA WITH OPTIC ATROPHY OF THE RETROBULBAR NEURITIS TYPE, AND LATENT PALLIDO-LUYSIAN DEGENERATION

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I. Introduction

In an earlier work (André-van Leeuwen and van Bogaert, 1942) we discussed the question of the relationship between the group of hereditary optic atrophies and that of the hereditary ataxias, on the grounds of a very suggestive clinical and pathological observation.

This concerned a boy who had shown stiffness of the lower limbs and a peculiar clumsiness from his earliest childhood. The fact that his vision was poor was noticed when he was 3 years old. He could find his way about until his death. When he was 6 years old, optic atrophy was discovered (Dr. Bauwens). When he was 8 he showed a bilateral Babinski sign, with tendon reflexes increased on one side and diminished on the other. His gait was slightly ataxic. He died from apoplexy at the age of 11 years. Pathological examination revealed bilateral optic atrophy affecting mainly the papillo-macular bundles, but extending well beyond them. There was, moreover, a slight but distinct affection of the pyramidal bundles, the posterior cords and the spino-cerebellar pathways.

Now this boy's mother, his grandfather and several other members of his family showed slight optic atrophy, the existence of which was not discovered until they were grown up. Also three of his four brothers and sisters showed, like their eldest brother, a severe affection of the optic nerve and a neurological syndrome of the type described by Behr.

In these children the ocular affection showed itself in their earliest childhood (in the two sisters the optic atrophy was established objectively at the ages of 4 and 3 years respectively, but loss of vision had already been noticed at 2 and 1½ years). However, the optic atrophy did not exist at birth (at least in the younger brother an ophthalmological examination at 7 weeks, by Dr. Bauwens, showed that the discs were pale, but had not the atrophic appearance observed later). Perimetry in the elder girl at the age of 13 years showed a very dense central scotoma of about 20 degrees diameter, with moderate depression in the rest of the field of vision. In the next eight years the visual defect did not change.

The neurological symptoms were also observed very early (at 4 and 3 years in the two girls). In the elder they consisted chiefly of hyperactivity of the tendon reflexes. The second showed, in addition, moderate but distinct cerebellar symptoms. The younger brother showed no particular neurological changes at 6 months. At 5 years hyperactivity of the tendon reflexes and a bilateral Babinski sign had developed. In all three children the feet became more or less hollow towards the

age of 12 years. Apart from this the clinical picture remained practically unchanged during the sixteen years the patients were followed.

Thus, in the third generation of the Del. family the affection of the optic nerve which had until then been very mild and isolated, was suddenly turned into severe optic atrophy, and became complicated by a syndrome of abortive hereditary ataxia (Behr's syndrome). This family therefore proves that *there is a direct link between the group of the hereditary optic atrophies and that of the hereditary ataxias.* However, many points in this problem still remain to be elucidated. First of all, are we to think that the "link" we were able to detect in this case is an exceptional manifestation of these relationships? Then, has hereditary optic atrophy (alone or associated with abortive hereditary ataxia) anything in common with the optic atrophy which is associated with fully developed ataxia? In particular, what are we to think of the clinical picture of these optic atrophies? Finally, what significance are we to attach to the obvious differences between the usual, very characteristic, mode of transmission of isolated hereditary optic atrophy and the genetic characteristics of strains with hereditary ataxia and optic atrophy?

The optic atrophy which is associated with hereditary ataxia was, as we know, formerly regarded as a progressive optic atrophy of the same type as that seen in tabes. More recent authors, however, express themselves much more cautiously on this point. Thus, in their important study J. Bell and Carmichael (1939) rightly note that the optic atrophy associated with hereditary ataxia seems to differ "in some important respects from that which comes under the category of Leber's disease" (notably in the absence of any history of sudden onset). But they emphasize the fact that this can, in the circumstances, only be an impression, because "reference to optic atrophy is often limited to the fact of its presence at the time of observation." When we recently (1948) went through the literature on this subject, we can only confirm these remarks. The few more detailed observations (which we shall sum up at the end of this article) do not, by themselves, allow us to form a firm opinion on the clinical characteristics *as a whole* which optic atrophy may show in this heredo-degenerative affection (and histological examinations are even rarer). Some more data must be collected before such a result can be achieved.

Judging by the small number of cases reported so far, Behr's syndrome seems to be rare. On the other hand, two families with optic atrophy have been described, in which one of the affected members also showed manifest hereditary ataxia. In one of them (Collier, 1912) the affection of the optic nerve differed considerably from the usual hereditary

optic atrophy (no central scotoma; production of amaurosis, or nearly complete amaurosis, in certain cases). The family described by Ferguson and Critchley (1929) consisted of a sibship in which 4 out of 5 members showed optic atrophy of the retrobulbar neuritis type. In the youngest girl a syndrome of manifest hereditary ataxia developed some time after the affection of the optic nerve. In families with hereditary ataxia properly so-called, the time of onset of optic atrophy and its severity may vary to a considerable extent. (The same applies to the other components of the group of hereditary spino-cerebellar degenerations, to which, in our opinion, the hereditary ataxias belong.)

There are many transitional forms between families in which a marked neurological affection is accompanied by only slight involvement of the optic nerve and those in which optic atrophy dominates the clinical picture. From this point of view, *the Del. family finds its place, quite naturally, at one end (quite close to pure hereditary optic atrophy) of the chain thus formed.*

The most usual form of transmission of pure hereditary optic atrophy is characterized, as is known, by two principal facts: a marked predominance of males over females among the members affected, and the fact that only women (generally unaffected themselves) transmit the disease. In these relatively very rare cases the inheritance is dominant or simply recessive.

In the few families in which optic atrophy, isolated in most of the affected members, is accompanied in some by abortive or complete hereditary ataxia the inheritance is not of the usual, sex-linked recessive type. As to families with hereditary ataxia properly so called (or a closely related hereditary spino-cerebellar degeneration), in which one or more members show optic atrophy, the inheritance follows the same laws as usually govern the neurological affection itself. (Thus the inheritance is preferably dominant in Charcot-Marie-Tooth's amyotrophy and in hereditary ataxia of the Pierre Marie type; recessive in hereditary ataxia of the Friedreich type and in hypertrophic neuritis; and sex-linked recessive in Pelizaeus-Merzbacher's disease.) From this point of view the *optic atrophy* seen in these diseases differs considerably from the usual isolated hereditary optic atrophy, and seems to *behave as an integral part of the neurological hereditary degeneration.* Certain facts, however, deserve attention. It is remarkable that in families where optic atrophy is itself transmitted directly by affected males, the affection of the optic nerve is not pure but is accompanied or replaced, at least in certain individuals, by retinal lesions (families 71 and 72 of Sjögren, 1943; S. Brown's family, 1892). On the other hand in the Le. family (293) of Bell and Carmichael

(1939) and in family I of Sjögren (1943) the optic atrophy certainly seems to have been transmitted by males, but these were not affected themselves.

We would also stress the fact that, taken all together, cases of hereditary spino-cerebellar degeneration with optic atrophy show a distinct predominance in males (though much less marked than in hereditary optic atrophy). Finally, when one considers that in most of the published cases only the brothers and sisters, or at most the parents, have been examined, and that these cases, therefore, do not allow us to judge with certainty exactly how the disease is transmitted, one must admit that the question of genetics cannot be considered as settled.

II. Clinical Study

The case we are reporting here is one of hereditary ataxia of the Pierre Marie type, with strictly sporadic optic atrophy, and therefore provides no new information concerning the general aspect of the problem we are studying. On the other hand, it enables us to complete and define our knowledge of the clinical and histological characteristics of the optical affections which accompany hereditary spino-cerebellar degeneration. In addition, it provides interesting data on the extension of the spino-cerebellar lesions characteristic of the hereditary ataxias to the hypothalamic and striatal level, thus complementing our observation with J. Titeca (1946).

We have already alluded briefly to this case (Case 8) in our lecture on progressive pallidal atrophy (van Bogaert, 1946).

A. The Frey . . . Family (fig. 1)

On the father's side, the grandfather (I/1) died at 71 years from gastric cancer, and the mother at 37 years from a puerperal disease (I/2).

On the mother's side, the grandfather Mart . . . (I/3) died at 82 years from an unknown cause, and the grandmother Mart . . . (I/4) at 84 years.

The eldest sister of our patient's father (II/1), Puyp . . . has 5 children (III/1-III/5), of whom the 3 daughters suffer from asthma. Our patient's mother

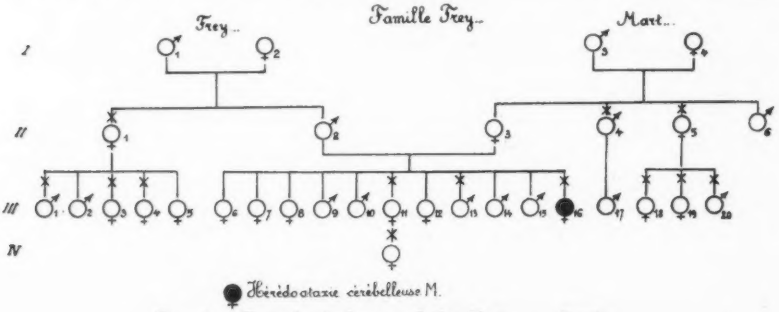

Fig. 1.—Genealogical tree of the Frey . . . family.

is still alive and shows no neurological or ocular disturbance. She has been examined: myocardial sclerosis and hypertonia. The father (II/2) died as a result of an accident at the age of 40 years: nothing special is known about him. 11 children were born of this marriage, 8 of whom died between birth and the age of 2 years, from unknown diseases. There remain one daughter, Agnes Fr. . . ., married, Labon . . . (III/11), who has a normal daughter (IV/1), one unmarried son, Urbain (III/13), mentally deficient without ocular or neurological disturbances, and a daughter, Célestine (III/16), our patient.

In the collateral branch of our patient's mother's family there is a brother Jean Marie Mart . . . (II/4), one son of whom has been examined and found normal; one sister, married De Breck . . . (II/5), who has two daughters with gastric disease but who, according to the physician attending them, show no neurological or ocular taint, and one normal son; one brother Hubert (II/6) who died at 53 years from angina pectoris and had no descendants.

In this family, therefore, we find no other case of hereditary ataxia than our patient, but her brother is mentally deficient and she lost 8 brothers and sisters before 2 years of age, from unknown diseases.

B. Case Report

Célestine Fr. . . , 20 years old.

Personal history.—Measles, scarlet fever and mumps in later childhood. From the age of 9 years it was found that she learnt badly, but she remained at school until she was 13. She was very inattentive and very emotional, clumsy in her gait, fell down often and her vision was poor. Towards the age of 12 years she had a very reeling gait. She complained of fatigue in the legs and arms. Her *speech* had become *incomprehensible*. She *articulated* badly and often swallowed the wrong way when she drank at all quickly. Between the 14th and 17th years she had a period of growth during which the disturbance of gait increased.

She was admitted to our department for the first time at the age of 17.

First examination, 10.2.38 (*A. van Bogaert*).—Pale, fair girl, rather tall (1·78 m.), slender, slightly uncertain gait, with heel bumping, and without much broadening of the base of support.

The hands are long, the fingers slender and very tapering, the palm hollow, the thenar and hypothenar eminences slightly wasted, camptocormia of the little fingers. Abnormal laxity of the joints. The feet are slender and short. The arch is hollow, as in Friedreich's disease. The toes are long and tapering. Cyanosis reaching to the upper third of the leg on both sides. The legs are cylindrical, the thighs thin and the pelvis narrow. Secondary sexual characteristics little developed. Slight cervical kyphosis. Sloping shoulders, neck "en coup de hache."

The tendon reflexes are lively, the abdominal cutaneous reflexes preserved, the plantar cutaneous reflexes produce flexion. No marked disturbances of superficial sensation.

Sense of position and pallæsthesia preserved in upper and lower limbs.

No sphincter trouble except before her periods, urgency of micturition. Preterminal hesitation in the finger to nose and heel to knee tests; not increased by closing the eyes.

Gross dysmetria in the test of putting the index finger on the examiner's finger, on a point marked on the table, etc. This difference in the dysmetria shown in movements made in reference to some external object and that shown in movements in reference to some part of her own body was observed several times. Romberg negative. No asynergia. Marked hypotonia of all four limbs with passivity and swinging of the upper limbs.

Hypermetria of both upper limbs in crawling.

Cranial nerves: The soft palate contracts normally. No disturbance of the movements of the tongue; the palatal and pharyngeal reflexes are normal. No disturbances of the pupils, of the sense of taste, or of facial and corneo-conjunctival sensation.

Lumbar puncture (3.3.38): Cells, 2; albumin, 0·30; colloidal benzoin reaction normal. Wassermann reaction negative, as also in the blood.

Viscera: The upper two-thirds of the right lung slightly dull on percussion. Radioscopy shows slight veiling, and the apex clears poorly on coughing. Heart drop-shaped. Tachy-arrhythmia without auscultatory signs. Blood pressure 110/90. Slight tenderness of the right ovary. Spastic entero-colitis. X-rays showed ptosis of both angles of the colon and a spastic state of the descending colon. Hæmorrhoids. Infantile uterus, retroverted and lateroverted to the left.

Second examination, 24.2.40 (*D. Louis-Bar*).—In October and September 1939 her vision suddenly deteriorated greatly at the same time as she suffered a sudden exacerbation of ataxia. For several weeks her gait was grossly drunken. There was a slight improvement in the visual and ataxic symptoms at the end of December 1939 (Ludo van Bogaert). Very unsteady gait, slightly spastic with heel bumping especially on the right. Turning round, and sudden changes of direction, are followed by loss of balance, sometimes with collapse on the floor. She also knocks against beds and seats, because of the loss of vision.

In Romberg's position, she falls backwards and often to the right. When standing she sways and makes small movements on the spot to regain her balance.

The finger-to-nose and heel-to-knee tests show gross dysmetria with decomposition and an intention tremor of great amplitude. On testing for asynergy, the loss of balance is very moderate. Diadokokinesis shows no marked changes. Hypotonia and swinging is shown in all four limbs. The patellar and tricipital reflexes are pendular.

The Achilles, medio-pubic, biceps and ulnar reflexes are very lively. The plantar cutaneous reflex is in the direction of flexion. The abdominal cutaneous reflexes are preserved. No disturbances of superficial sensation, but deep sensation in the lower limbs is not intact There are many mistakes in perceiving the position of the toes. Speech is drawling, poorly articulated and guttural; there are alternating dullness of speech and bursts of loudness. She easily becomes hoarse when speaking and drinking. The feet are more hollow, the hands clubbed with marked camptocormia of the little fingers, the terminal phalanx being flexed on the second.

The acrocyanosis reaches the knees and elbows.

The *visual acuity* (Maria André-van Leeuwen) is reduced on both sides to counting fingers at 2 metres. Quantitative perimetry is impossible; using the confrontation method, the limits of the field of vision do not seem greatly reduced. In the middle regions colour is recognized. White and coloured 5/500 points are not perceived in the centro-cæcal region, however, but they are on the nasal side of the point of fixation.

The fundus shows atrophy of the temporal sector of the disc on both sides, the nasal part being normal in colour. The retina and vessels show nothing worthy of note. The movements of the eye are normal. No nystagmus. The pupils are equal and normal and are large. The reaction to light is normal in both eyes.

Course.—During the following months speech deteriorated further. The girl walked little and complained of increasing fatigue. On April 19, 1941, at about 10 a.m., she suddenly felt ill, with a tendency to faint, dyspnœa, disturbances of speech and perspiration on the whole upper half of the body to the borders of the capillaries, and to the roots of the hair at the back. She complained of tingling in the neck and both upper limbs, and of the chest down to D8 - D9, in front and at the back.

On examination on 20.4.41 (D. Louis-Bar) it was found that she could not stand. As soon as she was set on her feet she sagged and collapsed, but in bed she still

had some muscular strength. Her movements were so clumsy that she was unable to pick up any object, large or small, in her hands, though some segmentary muscular strength was preserved; she could grasp a hand with some power if she was guided. On Colin's dynamometer she achieved 25 with the left hand and 35 with the right. Her clumsiness in using her hands arose from a disturbance of deep sensation. In all four limbs the sense of position of the whole limb and of its segments was severely impaired. She was unable to describe their position, yet she could localize exactly the points where she was touched. No disturbance of the sensations of heat or touch, either on deep pressure or with the tuning fork. The tendon reflexes were considerably weakened in the upper limbs. There was a bilateral Babinski sign, and the abdominal cutaneous reflexes had disappeared. There were disturbances of the sphincters (incontinence of urine and flatus) but she was aware of their passage. She uttered sounds, but no intelligible words, and swallowed the wrong way, especially when drinking. The pulse was irregular. Protrusion of the tongue was impossible, but slight side-to-side movements were preserved. The sense of taste could not be tested. The palatal reflex was abolished, the masseteric and pharyngeal reflexes preserved. During the following days her condition improved, but the disturbances of deep sensation persisted; the movements of the tongue improved and her speech became more intelligible. The difficulty in swallowing improved so far that on April 25 she could again take the same food as the other patients.

Third examination.—We saw her again (van Bogaert) on 4.5.41, and noted at that time very marked dysmetria in the finger-to-nose and heel-to-knee tests, this time aggravated by closing the eyes; the limbs were literally thrown in all directions as soon as she shut her eyes, so violently that she sometimes hurt herself.

Severe changes in deep sensation up to C2; even rotation and flexion backwards and forwards of the neck were poorly recognized. No number was recognized below C1, whereas this test had previously given satisfactory results.

Sensitivity to touch, heat and pain seemed intact.

The tendon reflexes were abolished in the upper and lower limbs. The corneo-conjunctival reflex was intact.

The cutaneous abdominal and plantar reflexes were normal. The movements of the tongue were practically normal. Only extreme protrusion and extreme lateral movements were still hampered. The palatal and pharyngeal reflexes were present. The voice, however, remained nasal. *Lumbar puncture* gave a clear fluid, with 4 cells and 0·45 albumin.

She died on May 23, 1941, in a few minutes, with cyanosis.

This girl's neurological affection must be regarded as a hereditary ataxia of the Marie type, in spite of its sporadic character and early onset, the first disturbances going back to the ninth year. During the whole course of the disease, excepting the last two months, the tendon reflexes were very lively. Apart from the cerebellar ataxia, the most striking signs were the dysmetria and intention tremor and the disturbance of speech.

This cerebellar ataxia was combined with an ophthalmological picture which was considered from the first to be a bilateral optic neuritis. It is impossible for us to locate exactly the beginning of the optic nerve lesions. According to the mother, the patient's vision was poor even in her school days. However, it was not until 1939 that severe disturbances of central vision set in, suddenly, in the course of a period of acute deterioration

involving both the cerebellar and the optic systems. They remained stationary during the two remaining years of the patient's life.

We had regarded the exacerbation in April 1941 as a rapid advance similar to that of 1939. As the tendon reflexes had disappeared and the patient showed at the same time a gross tabetic ataxia, we supposed this progressive phase to be a radiculo-spinal localization of the degeneration, completing the picture of hereditary ataxia, but in the sense of Friedreich, of which the trophic disturbances observed from the first (club hands and feet, cyanosis) were reminiscent. As a matter of fact, the histological study showed that this was not so, and that the exacerbation of 1941 must be interpreted differently.

C. Anatomical Study

Autopsy, 23.5.41, eight hours after death (L. van Bogaert): Lungs œdematous and engorged with blood. The upper two lobes of the right lung showed lesions of fibrous tuberculosis with a peribronchial primary lesion. Pleurisy of the right apex. Numerous adhesions between the lung and the diaphragm. The two pleural cavities contained about 150 c.c. of fluid. Heart: nothing worth noting. The liver and gall-bladder showed no particular changes. Tuberculosis of the mesenteric glands. Numerous adhesions between the ileum and the omentum. Sclerotic degeneration of both ovaries, uterus retroverted and fixed in Douglas's pouch on the left by strong bands. Right hydro-pyonephrosis.

Macroscopical appearance of the brain.—On looking at the lower surface of the fresh brain, the smallness of the cerebellum, the brain-stem and the chiasma, and the thinness of the optic nerves, are at once apparent. The cortex shows no abnormality. The vessels of the circle of Willis are supple. The pituitary is of normal size. No chronic leptomeningitis. No œdema found on palpation.

After hardening, the brain was cut into vertical transverse sections; small blocks were taken from the right hemisphere, the left being kept for a possible study of the optic tracts in large serial blocks.

The cerebellum is small: on section one already recognizes atrophy of the dentate nuclei. The peduncle shows relative atrophy of the cap. The central grey nuclei show nothing special. The cerebral white substance is normal in consistency. The spinal cord also shows no particular change and the roots are of normal size.

Microscopical study (I. B., 8/41).

Technique: Spielmeyer, cresyl violet, scarlet red, hæmateineosin, and van Gieson staining on frozen blocks. Nissl and Weill staining of large blocks embedded in celloidin.

Muscles: No important lesions. Some bundles show simple atrophy.

Nerves: In places, the intramuscular endings show interesting lesions. The axones are rarefied. Hypertrophic Schwann's cells surround fragments of axones and myelin debris, and are sometimes enormous. In other places they are fenestrated and surround the scattered myelin fragments in a syncytial form resembling what is seen in hypertrophic neuritis (fig. 2, p. 361). The endo- and perineurium are of normal appearance. In specimens treated with van Gieson's stain the walls of the vessels are slightly thickened and fibrous. These lesions are partial, for the trunks of the radial, median, external popliteal branch of the sciatic, sciatic and saphenous nerves which were examined showed no characteristic lesion.

Spinal ganglia: Nothing to note.

Roots: No difference between the posterior and anterior roots.

Spinal cord: Throughout the lumbar, dorsal and cervical cord (fig. 3): lighten-

ing and gliosis of the column of Goll, and, to a lesser degree, of the ventral cerebellar tract. No fatty debris. Cytological specimens show diffuse rarefaction in the anterior horns, with disseminated gliosis in the Holzer sections especially in the anterior-median groups and around the ependyma.

Transitional spino-bulbar zone: The focus of central and symmetrical necrosis which has been described elsewhere on the basis of serial sections (D. Louis-Bar, 1946) will not be described, only the systematized lesions being mentioned here. The pyramidal pathways are intact, the piniform decussation is very much lightened, the fibræ propriæ of Goll's and Burdach's nuclei less so. This atrophy of the nuclei of Goll and Burdach is seen again in the Holzer sections as is the sclerosis of the piniform decussation and of the arcuate nuclei. The olivary bodies, of which the lower part is seen here, show extreme sclerosis for the patient's age. In the next section degeneration of the medial lemniscus, of the internal and external arcuate fibres of the capsule and of the olivary hilus, of the dorsal and ventral folds of the principal olivary body and of the paroliva. Both hypoglossal nuclei show slight rarefaction of the fibræ propriæ, with gliosis and moderate cellular rarefaction. These lesions are probably secondary to the vascular involvement of the nucleus a little lower down. The same applies to the lesion of the dorsal nucleus of the spinal accessory nerve.

Median bulb: Marked rarefaction of the bulbar olivary bodies, especially in the dorsal lamella and parolivæ, with gliosis (fig. 4). The arcuate nuclei are a little better preserved. No marked cellular gliosis. Isolated cellular lesions (chromatolysis, lipid overloading) in the nucleus ambiguus on both sides. In sections through the upper part of the olivary body the rarefaction of the arcuate systems is less evident, the gliosis remains dense, the nuclei of the tenth, eleventh and twelfth cranial nerves are intact.

In the *inferior part of the pons* the pallor of the medial lemniscus of the posterior longitudinal bundle, of the predorsal fibres, etc., and that of the superior cerebellar peduncle are continued. Cellular lesions of the motor nucleus of the trigeminal nerve on both sides, with gliosis. On one side, these lesions are very pronounced, and are accompanied by glio-vascular proliferation forming an actual nodule with a tendency to necrosis. These lesions reappear in sections showing myelin.

The *ponto-peduncular transitional zone* presents no abnormality.

The *cerebellum* shows moderate atrophy of the whole organ, the amygdalæ are less affected on both sides (fig. 5A). The vermis is as much thinned as the mediodorsal surface. The white substance is well preserved, though a little less broad than usual. The dentate nuclei are severely affected: their lamellae are reflected over a hilus which is pale, and the markings of the lamellar folds are blurred in the demyelination of the afferent fibres and of the hilus. The cortex is uniformly altered (fig. 5B); Purkinje's cells are reduced to a quarter (fig. 6), and, in places, to a tenth of their normal density, both in the dome of the lamellæ and at the bottom of the furrows. The granular layer is intact except at three points, where it is slightly pale as in lamellar sclerosis. The myelinated fibres are preserved. Both components of the dentate nucleus are completely denuded of cells (fig. 7). The embolus and the globulus show similar rarefaction, but the ventral parts of the roof nuclei are preserved. The hili and the afferent fibres to the dentate nucleus are uniformly rarefied. The system of fibræ propriæ of the lamella are destroyed. Considerable cellular gliosis in the lamella, hilus and around the nucleus dentatus, markedly fibrillar gliosis in the hilus, but in the lamella and there are many astrocytes with large processes, forming a real network extending into the medullary laminæ, showing that the process here is still active. This same progressive, mainly perivascular, fibrillary gliosis, is also found in the regions of dichotomy of the lamellæ. In Bielschowsky specimens a certain number of empty "baskets" are observed in addition to the normal ballooning, and also abnormal impregnation of

the fibrils in Bergmann's glia. Some Purkinje's cells show "branched" swelling of a dentrite (fig. 8).

Cerebral peduncle: The section passing through the decussation of the cerebellar peduncles shows them and the lemniscus medialis to be severely affected, and the predorsal fibres, the posterior longitudinal bundle, and the thalamo-olivary tract relatively well preserved (fig. 9A). This is confirmed in the Holzer preparations where it can be seen that these last structures are not quite normal (fig. 9B).

In the *sub-optic and optostriate nuclei* what strikes even the naked eye on myelin and glial sections is the pallor of the corpus subthalamicum (Luys's) and a slight pallor in the external part of the pallidum on both sides. Gliosis is very dense in the whole of Luys's body from front to back. This nucleus has lost the greater part of its cells. Those which remain are rounded and swollen. The external segment of the pallidum also shows moderate gliosis and marked cellular rarefaction. The medullary layers on both sides are visible because of gliosis. The anterior ventral nucleus and the deep prolongation of the reticular zone show abnormal glial density, but the cells are preserved. The red nucleus shows moderate loss of cells, but frank cellular and fibrillar gliosis. The putamen and locus niger are intact. The optic layer and the pulvinar show no lesions either. Illustrations showing these lesions have been reproduced in another paper (van Bogaert, 1946), on pallidal atrophy, to which the reader is referred.

The *centrum ovale* shows in a few, rare places a small degree of perivascular glial infiltration.

The *cortex* is well preserved. In the frontal and parietal regions there is marked infiltration of the molecular layer with macro- and microglia.

The *optic system* could be studied in its entirety.

The *eyeballs* were cut into serial sections in the horizontal plane, and stained by van Gieson's method. The external membranes, the internal layer, and the pigmentary epithelium are normal. The layers of cones and rods and the external granular layer, and the bipolar cells show no changes except those due to rather late fixation. The bunch of central cones, in particular, is intact. The ganglion cells are present in the usual number in the whole retina, except in the macular region, where they form only a single layer of cells, or rarely two. In the horizontal sections passing through the uppermost and the lowest parts of the optic nerve the layer of optic fibres shows no particular change. In the more central sections, taking in the fovea (fig. 10A) and the perifoveal region, the layer of optic nerve fibres coming from the nasal side is normal, as are the penetration of these fibres into the papilla and their path in the intrabulbar part of the optic nerve. The layer of optic nerve fibres on the temporal side is much reduced in size and shows an increase in the density of the glial nuclei (fig. 10B). The temporal part of the disc is excavated. The lamina cribrata on this side is interrupted at only a few points by fine bundles of fibres. It has been transformed into a glial and connective membrane with almost continuous transverse striation, whereas it is normal on the nasal side. Behind this layer the bundles of optic nerve fibres are diminished in volume, separated by thickened septa in which vessels and cells are denser than usual. The central vessels have slightly thickened walls.

The *optic nerves* show a clearly defined zone of degeneration, which corresponds to the papillo-macular bundle and does not extend beyond it. In serial transverse sections (figs. 10C, D,) this degenerate zone which, near the eye, is shaped roughly like a wedge with the base outwards, may be seen to penetrate gradually to the inside of the nerve, turning on its own axis in such a way as to occupy the central part of the lower half of the nerve, the part which was originally to the outside now being on the lower side. In this zone the fibres of the optic nerve are very much reduced in size and demyelinated and are the seat of cellular gliosis. No fatty substance stained by scarlet red.

In the horizontal sections of the *chiasma* (Nissl, v. Gieson) (fig. 10E), the juxtachiasmatic part of the optic nerves shows, on the left, two distinct streaks of gliosis and increased vascularization, one central and the other along the inner border of the optic nerve. On the other side only the central zone of gliosis is clearly visible. It also follows the course of the optic nerve fibres. At the decussation itself the anterior third and the greater part of the posterior third are normal; the central part is affected by distinct gliosis following the transverse course of the fibres. The lateral parts of the body of the chiasma also show an increase in the number of glial nuclei, chiefly in the antero-posterior direction. The parts of the optic tract appertaining to the chiasm, which are cut at the supra-optic level, do not show distinct gliosis. It is evident that these sections, instead of being strictly horizontal, have touched the optic nerve at a more dorsal level than the optic tract. On the left they have shown the degeneration of the direct (central) and crossed (internal) components of the papillo-macular bundle of the optic nerve as individualized by Rönne (1910). They show, moreover, the great dispersion of the macular fibres at the chiasma, which has been stressed by many authors.

In the transverse sections of the *optic tract* (fig. 10D), the zone of degeneration again occupies a well-defined region, the remainder of this structure being perfectly normal. Its position corresponds with that described especially by Rönne. In the anterior parts the bundle is in the form of a wedge whose base coincides with that of the optic tract, and whose apex is directed toward the free border of the tract. Further back, the extremity of the degenerated streak, directed at first towards the base, not only follows the rotation of the tract by turning towards the internal side but also leaves its central position to become dorsal. The degenerated bundle then takes a horizontal direction, being separated from the upper border of the tract by only a thin layer of normal fibres. It keeps its point of attachment to the base of the tract. The histological characteristics of the degeneration differ from those met in the optic nerve only in the absence of septa. The fibrillary gliosis (Holzer) is more distinct here. A figure passing through the median level of the *external geniculate body* shows no lesions of its ganglion cells, but very distinct gliosis situated in its centro-dorsal part (fig. 11).

The *geniculo-calcarine region* and the occipital cortex are normal.

D. Discussion

The change revealed by histological study of the neuraxis can be arranged in the following groups:

(1). Symmetrical centro-medullary necrosis of the bulbo-spinal transition zone and of the lower and dorsal part of the bulb following thrombosis. These lesions are recent. Recent cellular lesions in the nucleus ambiguus, magnocellular nucleus of the reticular formation and the motor nuclei of the trigeminal nerve.

(2). A systematized affection consisting of degeneration of Goll's tracts, and, to a less extent, of the ventral spino-cerebellar tracts: severe degeneration of both bulbar olivary bodies—cortical cerebellar atrophy of the cerebellifuge type—gross atrophy of both dental nuclei, the embolus and to a lesser degree of the roof nuclei—a slight affection of the red nuclei—severe atrophy of the bodies of Luys—a moderate degree of atrophy of both corpora pallida.

(3). Symmetrical degeneration of both papillo-macular bundles.

showing the same histological characters as the systematized affection described above.

The significance of the necrosis of the bulbo-spinal transition zone, of the latent pallido-luysian atrophy and of the degeneration of the papillo-macular bundle will be discussed specially.

There is no lack of cases showing fairly acutely progressive phases for which no valid explanation can be given. These exacerbations, moreover, are reminiscent of the onset of Leber's disease. Anatomical study (D. Louis-Bar, 1947) shows, in addition, that in this case the most serious exacerbation was due to symmetrical bulbar necrosis in the territory of the anterior spinal artery, a lesion with all the characteristics of softening, and which cannot be confused with the other degenerations. Now the blood vessels of the optic nerve, of the chiasma and of the spinal cord were, in our case, perfectly healthy, and it is necessary, in order to explain the lesions, to resort to functional vascular disorders. This is the only focus of necrosis to be found in the whole central nervous system of the patient, and if this vascular mechanism can be rightly invoked as far as the final cervico-bulbar exacerbation is concerned, it has not been demonstrated, nor can it be demonstrated, as an explanation of the other exacerbations, especially that affecting the optic pathways. Our case is not unique from the point of view of the role of functional vascular disorders in the hereditary degenerations, and in Mollaret's (1929) well-documented work there is a case of Friedreich's disease with gangrene of the lower limbs in which examination showed no lesions of the veins or arteries, but only the presence of clots obliterating the arteries, recent clots, and infarcts of the liver and spleen. The cardiac valves were not affected. The complete arrhythmia observed was not associated with any particular electrocardiographic changes, but tests of the vegetative system revealed a marked vagal involvement which Mollaret believes to be due to the bulbar lesions. May it not be assumed that in our case the bulbar necrosis is the consequence of some such vegetative disturbance, in the same way as certain nervous symptoms which have so often been seen in the heredo-familial optic atrophies as well as ataxias, such as syncope, acrocyanosis, arrhythmia without myocardial insufficiency, epilepsy, etc.

We shall not again discuss, in the present paper, the *co-existence of Luyso-pallidal atrophy and spino-cerebellar degeneration* of which the first two known cases were reported by Greenfield (1934) in rapidly progressive cases, and certain peculiarities of which one of us has already mentioned in another paper (van Bogaert, 1946).

This same Luyso-pallidal atrophy is in the foreground of the spino-ponto-cerebellar lesions in the case of heredo-degenerative hemiballism

studied with Titeca (1946). Finally, pallidal atrophy may be seen in a familial form of hereditary cortical cerebellar atrophy (van Bogaert, 1947). This last patient showed, apart from a classical Marie-Foix-Alajouanine syndrome, only a few slight clonic movements of the two upper limbs. One wonders if it is not the fact that the Luyso-pallidal degeneration was quantitatively and chronologically in the foreground of the associated spino-cerebellar lesions (in the case of hemiballism) which was responsible for its becoming manifest; and the fact that it appeared late and in the background of the cerebellar and spino-cerebellar degeneration which is responsible for its clinical latency in the present case and in the familial affection to which we have just referred. It is not impossible that some importance must be attributed to a special resistance of the nervous system in the family where the pathological mutation breaks out.

The most striking feature in the optic nerve degeneration in this girl is its *strict limitation to the papillo-macular bundle.* As far as we know the "retrobulbar neuritis" type of optic atrophy has never before been described in a case of hereditary ataxia. It is true that, as stated above, the number of cases in which sufficient details of the occular affection are given is relatively small; in spite of the great frequency of optic atrophy in this disease.

We have found altogether about twenty (families) of which we give a summary below.

Some of these cases are striking by reason of the severity of the optic nerve affection, which gave rise to marked visual disturbances, affecting central and peripheral vision.

Thus Bäumlin (1901) reports the case of two children (M.) whose healthy parents were consanguineous in the fourth degree. In the brother the ocular instability was noticed by the parents at the age of 1 year. Until he was 7, he could run easily: then he began to fall often. At 14, he already showed serious neurological symptoms. In his first years at school, it was noticed that his vision was poor: "the letters got blurred." The first examination, at the age of 10 years, showed "slight neuritic atrophy"; the visual acuity was 1/100 in both eyes. Four years later, a visual acuity of 5/100 was noted on both sides. The field of vision for white seemed greatly restricted. The discs were whitish-green, their outlines clear, and the arteries were slightly narrowed. The elder sister, according to the history, showed no abnormality up to her 15th year except slight internal strabismus and some difficulty in reading small writing. The neurological symptoms were said to have set in at the age of 15, followed by diminished vision. As a matter of fact, at 13 years her vision was 5/100 in both eyes; there was slight neuritic optic atrophy (Siegrist). Four years later she showed moderate neurological

disturbances; ocular examination showed the fundus to be in a similar state to her brother's. Visual acuity was 0·075, and the field of vision was reduced concentrically. In Holmgren's wools, the brother and sister recognized blue and yellow (from a very short distance); red and green were recognized only when the colours were strongly saturated. The field of colour vision could not be determined.

In the family described by Stewart (1912), three children out of four were affected by Marie's hereditary ataxia (no other case in the family, no consanguinity mentioned). The eldest girl had never walked well, and at 28 years she could only advance with support. Her vision was reduced to light perception, and was said never to have been better. In the second, a boy, vision had also been affected all his life; his gait was said never to have been normal, but at 19 years he could still walk alone. The third, a boy, had been able to read and write. He was said to have walked normally up to the age of 7 or 8 years. At 14 years he could count fingers at three feet and showed slight neurological signs. In all three the optic disc was atrophied.

We have ourselves (1948) had the opportunity of seeing two children (family van Tilb.), suffering from Friedreich's ataxia, in whom the visual disturbances were noticed at the ages of 8½ and 6 years respectively. At 9 years the elder boy showed marked atrophy of the disc; he could count fingers at 5 metres and showed distinct and complete restriction of visual field. During the next eight years we watched the advance of the visual defect, which was fairly uniform in the various regions of the visual field (1940: the isopter 2·5/1,000 lies at about 50 degrees; 5/1,000 at ± 35 degrees. 1946: 2·5/1,000 not recognized at all; the isopter 5/1,000 lies at about 15–20 degrees; 10/1,000 at ± 35–40 degrees. 1948: the position for 5/1,000 is at about 8–10 degrees, for 10/1,000 at 15–20 degrees, for 50/1,000 at ± 35 degrees). In his younger sister the ocular affection was still earlier and more severe. Now, at 16 years of age, she has only faint vision in the region of the point of fixation. Beside these cases of early, severe and soon complete optic atrophy, other cases are striking, on the contrary, by the apparent disproportion between the affection of central vision, which is severe, and that of the peripheral parts of the visual field, which are much slighter. Thus Bergmann (1921) described the case of a man of 47 years (M.) in whom neurological symptoms set at the age of 30 years. Two years later examination of the fundus showed no particular changes. Later his vision was said to have failed gradually, especially after the 37th–38th years. At 43 years he could count fingers at 2·15 metres (visual acuity not improved by glasses), and the visual field and colour sense were normal. Four years later the visual acuity was ± 5/60 in both eyes. Examination of the fundus showed some pallor of the discs, especially on the temporal side: "the fields of vision were slightly diminished."

In the family described by Sanger Brown (1892) five individuals were examined by the author himself and by ophthalmologists. We are repeating here the reports of the fundus examinations and of the tests of vision. In Case 18 the neurological and visual disturbances set in at 18 years. At 30 years "vision is 20/100 in either eye. Snellen No. 5 can be read, though with difficulty, at 8 inches in an ordinary light, much more easily in a dim light. The ophthalmoscope shows decided blanching of the optic discs and lessening of the calibre of the arteries, with slight but distinct atrophic changes in the retina. There are only slight peripheral limita-

tions of the field, and almost complete colour blindness, red only being distinguished with any degree of certainty." Case 10, a second cousin of the last, and, like him, examined by Dr. Montgomery, did not notice any visual disturbance until he was 35 years old. Three years later the result of examination of the eyes was identical with that in Case 18, mentioned above. Case 19, Case 18's sister, noticed at 23 years that "vision was indistinct in a bright light, and she would move back from the window when reading." Three years later ocular examination by Dr. Wook revealed "vision is 20/80 and Snellen No. 3 is read well enough at 10 inches. Patient reads much better in a dim light. The average expert would pronounce the fundus normal without knowing anything of the condition of the vision. The colour sense is not much affected, and there is some peripheral limitation of the field of vision." In her younger brother (Case 20) the visual disturbances began at 20 years. He was seen at 24 years by the same oculist as his sister. The result of the examination was identical. This patient was later followed by Barker (1903). Until his death six years later he was able to read ordinary print. (The histological examination of the optic nerve is not mentioned in the text.) Finally the mother of Case 10 was seen by Dr. Montgomery. She was supposed to have been able to read good print up to the age of 58 years, then her vision deteriorated quickly, first in the right eye and then in the left. At 67 years she could only perceive light, and the optic discs were atrophied. Case 6 was not examined, but had also, during his life, suffered from nyctalopia and a marked reduction of vision (inability to read). Histological examination showed the optic nerves "free from degeneration and also from neuroglia overgrowth" (A. Mayer, 1897).

In this family the relative severity of involvement of central and peripheral vision varied from one person to another. In most of them, however, manifest nyctalopia was mentioned. In the absence of disturbance of the ocular media, it is difficult to see what is the cause of this nyctalopia: unless it be the fact that the defect in vision lies, at least preponderantly, in the central regions of the visual field. But is this defect dependent on an affection of the optic nerve or on true (macular) retinal lesions, or to a combination of both? Did these two kinds of lesions perhaps alternate in this family? The information given by the author, remarkable as it is considering the date, do not allow us to judge. Besides, it must be noted that S. Brown's family is not the only one which raises the problem of the interrelation of optic and tapeto-retinal affections in systematized hereditary degeneration.

In the following cases we find a mention either of "concentric restriction" of the field of vision, apparently of little extent compared with the loss of visual acuity, or a slight impairment of central vision, the field of vision being normal.

Family II, described by Jendrassik in 1897, contains two affected children. In the brother the disease set in about the 7th–8th year. Four years later his visual actuity was 1/6, and the field of vision scarcely restricted. The optic discs were clearly discoloured and the arteries a little constricted. His sister was 8 years old (onset at 6 years). Her visual acuity was slightly diminished, the colour sense and visual fields apparently normal. The discs were distinctly discoloured, bluish white, and the vessels normal.

In one of the two brothers studied by Young (1934) the disease showed itself at the age of 5 years by loss of vision. At 10 years his gait became uncertain. At 21 years vision was 6/33 in both eyes (not improved by glasses). On perimetry the limits for white were: right eye, sup. 40, temp. 75, inf. 80, nas. 60; left eye, sup. 40, temp. 70, inf. 60, nas. 45. The blind spot was slightly enlarged. In the elder brother (23 years old) the visual disturbances were said to have begun only two and a half years earlier (onset of neurological symptoms at 13 years). Visual acuity was 6/30 in both eyes; the visual field for white was: right eye, sup. 40, temp. 90, inf. 75, nas. 60; left eye, sup. 50, temp. 77, inf. 70, nas. 55; blind spot slightly enlarged. The author also gives the limits for colour vision, which were not very different from those found in normal people (at least if the indices were of the usual type). In both brothers light sense (by Birch-Hirschfeld's method) was only slightly diminished. Both showed distinct optic atrophy, more marked in the external segment.

In P. de Mello's (1943) family, the eldest of six children (two of whom were normal) died blind at 22 years of age. Disturbances of gait set in at 13 years, and later there developed a syndrome of Ramsay Hunt's cerebellar dyssynergy with progressive loss of vision. In the fourth, similar nervous and mental symptoms appeared simultaneously with loss of vision (at about 12–13 years). Optic atrophy was found at 14 years. Four years later he could count fingers at 3 metres with both eyes. Visual field (white 5/330): right eye, sup. 38, temp. 55, inf. 40, nas. 40; left eye, sup. 40, temp. 75, inf. 40, nas. 40. The two youngest sons (17 and 16 years old) showed temporal discoloration, especially on the right, with slight constriction of the arteries. They were free from neurological symptoms (apart from weakening of the patellar reflexes).

W. Sinkler (1906) reported the case of a boy of 13 years (case III) in whom visual acuity was 3/4, the visual field for form was normal, but for colours it was slightly restricted. The discs were oval, and the external half seemed pale.

Benelli, Zuccarelli and Donati (1927) also observed a man 27 years old (Friedreich probably familial, consanguineous parents) and they mentioned that the disc was normal in the left eye, whereas the right disc was very pale in the temporal zone. The fundus and macula were normal in both eyes. Visual acuity 7/10 in both eyes, fields of vision normal, blue and green were confused. (It must, however, be noted that this patient, whose neurological disturbances began at 10 years, later contracted syphilis.) De Mello's observation alone gives some quantitative perimetric data. The severe central involvement was accompanied by a peripheral loss which was also very distinct, though seeming less severe. The other case reports give no information as to the

size of the markers used, which makes interpretation of the fields of vision difficult. Are all these cases to be regarded as "global optic atrophy," and as more or less uniform? Is a mental factor to be taken into account as well (it is well known how often hereditary ataxias are accompanied by mental abnormalities)? These various questions spring to the mind on rereading the old observation of Nonne (1892-1904), dealing with three brothers suffering from hereditary ataxia of the Pierre Marie type, with optic atrophy. In the second, Heinrich Stübe, the neurological symptoms began at 30 years of age, after a shipwreck. At the same time his vision was said to have gradually decreased. At 46 years visual acuity was 5/10. The visual fields for white and colours were distinctly restricted, green was only recognized hesitantly, red better, and blue best. The external half of the disc was pure white and the inner half greyish white. The outline of the disc was clear and the blood vessels normal. The youngest brother, who was worst affected, was not examined opthalmoscopically. He distinguished red and green poorly, and yellow and blue better. Anatomical examination showed that the optic nerves had undergone degeneration. The eldest, Fritz Stübe, began to have difficulty in walking at 14 years. Vision seems to have deteriorated gradually. At 49 years both discs were discoloured throughout, their limits were clear and the vessels normal. Visual acuity was 1/9 in the right eye and 1/6 in the left eye. Red was recognized by both eyes, but not blue or green. The visual field was diminished to about a half. Until his death, 8 years later, he showed "defective vision due to partial optic atrophy." Pathological examination showed an evident diminution in the size of the optic nerve, but, as can be seen easily in the figure illustrating the text, and in contrast to what might be expected from the clinical symptoms, the degeneration did not affect the nerve uniformly, the bundles in the central and lower central parts of the section being much paler and more shrunken than the surrounding bundles. The similarity of this picture with that found in the case published today is obvious.

We believe that the various facts we have been noting justify us in asking if the "retrobulbar neuritis" type is really as rare in hereditary ataxia as it seems at first sight to be. This question seems even more justified by the fact that in spastic paralysis, of which only a few cases associated with optic atrophy are known, such a type has been recognized.

Jendrassik (1897) published the case of two sisters, aged 18 and 10 years, whose parents and two elder sisters were healthy. In the elder, divergent strabismus and disturbances of gait set in at 10 years. At 18 years she could count fingers. Examination of the visual field showed a central scotoma of 5-10° (she could only see objects at the edge of the scotoma) whereas the peripheral part of the field was not appreciably restricted.

The colour sense was seriously affected; she could only recognize one or two colours, and that only in a small part of the visual field. Fundus: very marked optic atrophy. The disc was chalky white, its limits well defined; the arteries showed no changes. In the younger, the neurological symptoms began at 9 years. A year later visual acuity was 1/5, the field of vision distinctly reduced. She did not recognize colours at a distance of one or two metres. Fundus: marked atrophy of the discs. Apart from the internal halves, which still showed a pinkish reflection, they were whitish blue; the outlines were clear. The child could still read and write fairly well, and had not noticed, any more than her family had, that she had poor sight.

Recently (1948) one of us has defended the opinion that the syndromes of hereditary degeneration constitute mosaics which overlap not only our clinical frameworks, but also the arguments of topographical anatomy which one has tried to impose on them. There are so many intermediate links within a single group, from one case to another, within a single family, that the old view of Jendrassik (1902) is brought to mind. At the same time, in the interrupted chain of the neural abiotrophies certain links are observed to be very stable in certain families, occur very frequently, and correspond histopathologically to complexes of neuronal degeneration. To these links correspond morbid entities. *There is a very close affinity between the hereditary ataxias, familial spastic paralysis and Charcot-Marie-Tooth's amyotrophy. Generally speaking optic atrophy, which may occur in each member of this group, takes the same clinical form as that which we have encountered in the hereditary ataxias.* Two (perhaps three) well-defined types seem to merge from the sum of these observations.

In certain cases optic atrophy shows the quite typical picture of "retrobulbar neuritis." Vision is reduced surely, sometimes considerably (visual acuity from 1/4 to less than 1/100); there is a central scotoma and temporal discoloration of the disc. Sometimes an appearance of optic neuritis is described. A single report, that of Rouffinet (1891) (hypertrophic neuritis) gives a description of a paracentral scotoma, leaving the visual acuity intact. The peripheral parts of the visual field are generally little affected. Sometimes, however, the lesion seems to extend distinctly beyond the papillo-macular bundle, and a greater peripheral defect is reported. The onset of the optic nerve affection often dates back to childhood, but it may not appear until adult life. The intactness of the peripheral part of the visual field or the slightness of its deficiency (demonstrated thirty or even forty years after the onset of the visual disturbances) seem to point to an arrest in the development of the optic affection, or at least to little progressive tendency.

In striking contrast to this first type of optic atrophy, there are other cases, in which we see the optic atrophy rapidly become serious. The visual defect becomes so marked that all useful vision is abolished, and complete blindness may even be produced. In this stage the disc, which is generally of a pearly white colour, is atrophied throughout. In the rare cases where it has been possible to examine the visual field there has been a considerable concentric visual defect. At a less advanced stage central vision might perhaps be affected more than peripheral vision.

Again unlike the "retrobulbar neuritis" type in which the age of onset varies considerably, this *massive optic atrophy* seems always (at least in cases published so far) to show itself early. In certain cases it even seems to be congenital or at least to go back to earliest infancy (P. Stewart, 1912). Perhaps it shows itself at the latest at puberty.

Histological examination in one such case (Nyssen and van Bogaert) showed nearly complete demyelination of the optic nerves.

Finally, the third type is characterized by a more or less marked loss of visual acuity, a more or less intense *"concentric restriction"* of the visual field, and a history of a slow advance of the optic affection. This last type, however, is less clearly defined than the two first, and we do not know any histological descriptions which might correspond with this clinical picture.

The analogies there may be between the optic atrophies associated with hereditary spino-cerebellar degeneration and those forming part of the Leber's disease group need no comment. We would merely emphasize the fact that in both cases the optic atrophy shows itself at an early age and tends to be of a particularly serious type.[1] It must be noted, however, that these data are based on an insufficient number of cases to allow us to estimate how frequently the different forms show themselves. Moreover, they still need to be completed in many respects especially regarding the mode of onset of the visual disturbances and their usual course. These data are very difficult to obtain in this type of patient, often mentally affected and living in special conditions, as is well known to anyone who has had to carry out such investigations. However, *if one wishes to learn what place must be assigned to optic atrophy associated with hereditary degeneration in relation to isolated optic atrophy it is an essential preliminary condition to know exactly the different forms it may take.* Further research will certainly enable these data to be established, just as new, detailed familial investigations in strains showing hereditary optic atrophy or hereditary spino-cerebellar degeneration will, no doubt, throw light on the genetic aspect of this problem.

[1] The heredity is also of a special type here, in the sense that in all the cases we know of it is simply recessive, and there is no distinct predominance of affected males.

Conclusions

(1) Hereditary cerebellar ataxia of Marie's type may be accompanied by Luyso-pallidal degeneration in the same way as this may be seen in late cortical cerebellar atrophy (Marie-Foix-Alajouanine). In the cases observed by us, this atrophy was clinically latent, and this latency may be due to the fact that Luyso-pallidal degeneration represents a late phase in systemic degeneration, whereas in other families it is chronologically and quantitatively in the foreground of the degeneration of the spino-cerebellar, or even spino-ponto-cerebellar complexes. The significance and the clinical expression of this striatal extension of hereditary spino-ponto-cerebellar degeneration deserves the attention of observers in the same way as does the mesencephalo-cerebellar extension of hereditary extra-pyramidal degeneration. The first landmarks are placed by the olivo-ponto-cerebellar degenerations. Cortical atrophies may be a similar material of choice.

(2) It may be accompanied by systemic atrophy of the papillo-macular bundles, manifest clinically in the form of bilateral retrobulbar neuritis. Our researches confirm the earlier data regarding the position of this bundle in the optic tract. Systemic atrophy of the papillo-macular bundle has probably been observed before, in other cases of hereditary ataxia; but its frequency and its clinical forms cannot yet be fixed because of the lack of definite clinical and pathological documentation. Beside this we must place two other types: severe optic atrophy of early onset and global, slowly progressive optic atrophy. The cases of hereditary degeneration associated with the first and third types have no special distinguishing features, but in those in which the optic atrophy is of the second type, the neurological affection, whatever it may be, is more serious and appears earlier. In such cases the degeneration seems to affect several neurones at once, with interfamilial variations. At present, however, the documents which can be utilized are too few to allow one to think of drawing any more general genetic conclusions.

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ILLUSTRATIONS

FIG. 2.—Lesions of one of the intramuscular nerve endings "Fenestrated" appearance of the hypertrophic Schwann cells surrounding the debris of the myelin sheath. (Paraffin—van Gieson.)

FIG. 3.—Section of the lower cervical spinal cord, roots and spinal ganglia. Lightening of Goll's tracts and, to a lesser degree, of the ventral spino-cerebellar tract, especially on one side. Roots intact. (Celloidin-Weill.)

FIG. 4.—Gliosis of the bulbar olives. (Freezing—Holzer.)

FIG. 5.—Cerebellum, general view A The cortical atrophy is very moderate and diffuse (Celloidin—Nissl). B The white substance is hardly thinner than normal, but the dentate nuclei are severely atrophied, as are the systems of the upper cerebellar peduncle. (Celloidin—Weill.)

FIG. 6.—Details of the cerebellar cortex: "clivage" of the layer of Purkinje cells, proliferation of Bergmann's glia, rarefaction of Purkinje cells, very slight lightening of granules. (Celloidin—crésyl violet.)

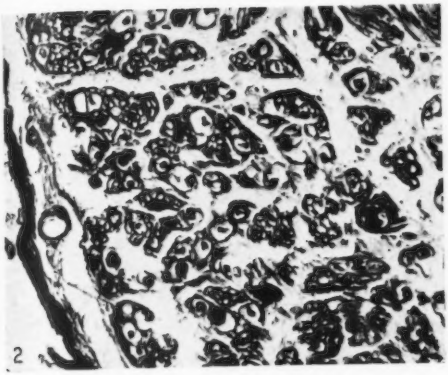
FIG. 7.—Detail of a microgyric lamella of the dentate nucleus. All the cells except an occasional atrophic one have disappeared; dense cellular gliosis. (Celloidin —Nissl.)

FIG. 8.—Swelling of a dendrite of Purkinje cells. Rarefaction of the tangential systems. (Freezing—Bielschowsky—Reumont.)

FIG. 9.—A Cerebellar peduncle: degeneration of the decussation of the cerebellar peduncles and of lemniscus medialis (Freezing—Spielmeyer). B Gliosis of this decussation of the superior longitudinal bundles of the predorsal fibres and of lemniscus medialis. (Freezing—Holzer.)

FIG. 10.—A Lesions of the retina at the fovea (Celloidin—van Gieson). B Optic nerve in the perifoveal region; though the layer of fibres from the temporal side is much reduced in volume and shows considerable density of the glial nuclei. The nasal part is looking normal. (Celloidin—van Gieson.) C Optic nerve, near the eye: vertico-transverse section showing the position of the papillomacular bundle. (Freezing—Spielmeyer.) D Optic nerve farther back. (Freezing—Spielmeyer.) E Optic tracts. Vertico-transverse section. (Freezing—Spielmeyer.)

FIG. 11.—External geniculate body. Ganglionic layers intact. Gliosis of the centro-dorsal part. (Celloidin—Nissl.)



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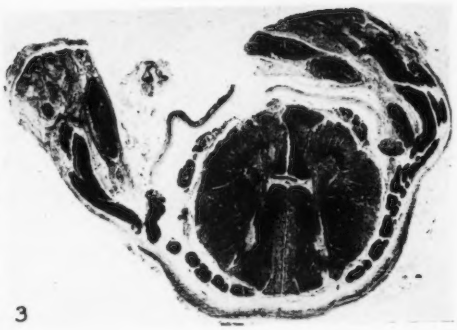

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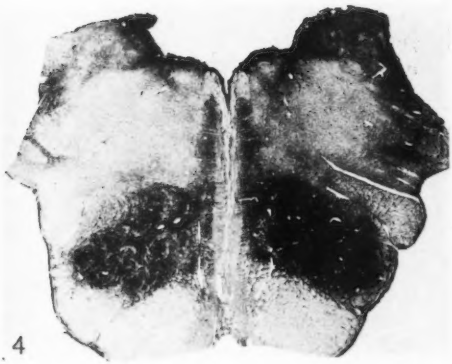

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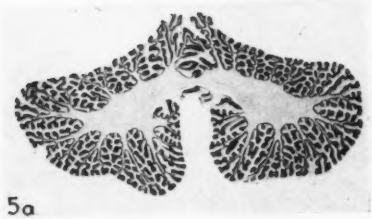

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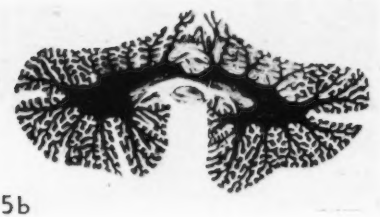

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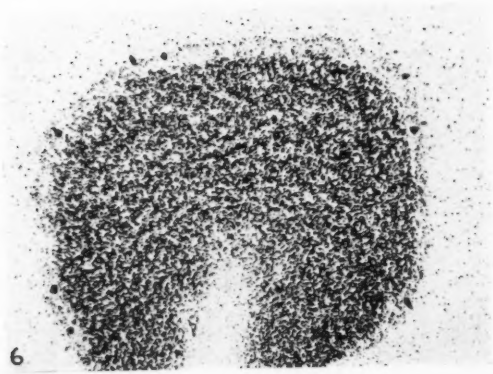

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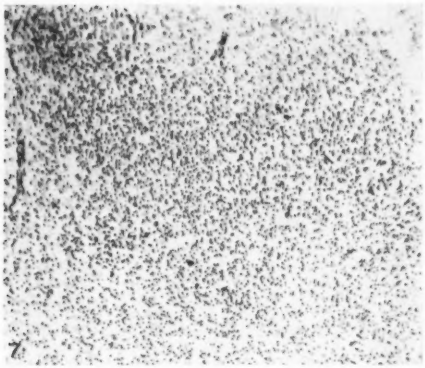

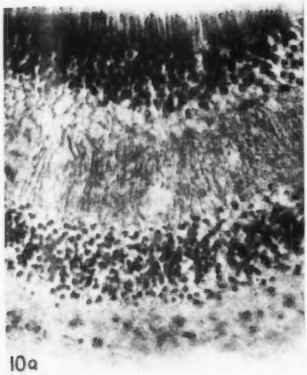

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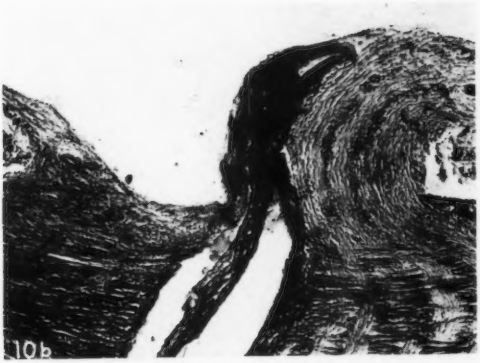

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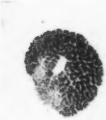

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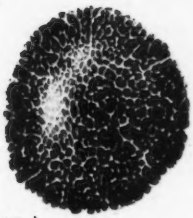

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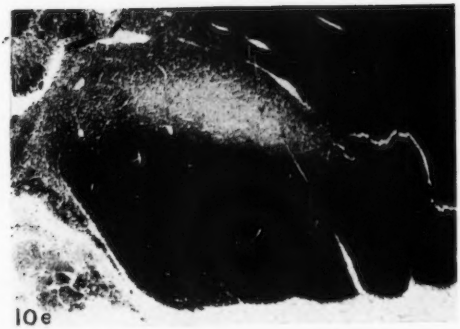

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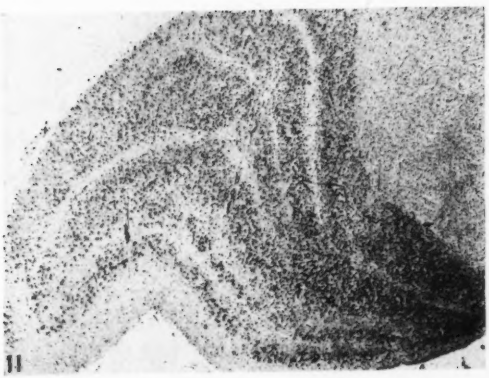

11

THE REMOTE REFERENCE OF PAIN AROUSED IN THE SKIN

BY

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INTRODUCTION

IT is now a commonplace that pain aroused by a stimulus originating in a viscus is frequently "referred" to an area of skin (Head, 1893; Mackenzie, 1909, and others). It has further been shown that the pain produced by the injection of an irritant fluid into deep somatic tissues, such as skeletal muscle, may be referred in this manner (Kellgren, 1938; Lewis and Kellgren, 1939; Inman and Saunders, 1944). The present paper is an account of some observations made on the reference of pain from one area of skin to another.

METHODS

Some thirty healthy young adults were informed of the object of the investigation, and were asked to report the results of pinching accessible skin areas between finger and thumb. In all, eight subjects discovered the presence of one or more cutaneous "trigger points," stimulation of which led to the appearance of pain elsewhere in the skin, and in each case these points were investigated experimentally. The majority of the work was, however, done on 18 such points occurring in four subjects (*see* table).

Painful stimuli applied to these points included pricking with a fine needle, pinching by a pair of square-ended epilation forceps, injection of hypertonic saline, local heat, and faradic stimulation from a physiological induction coil. In the last case a sharp-pointed electrode was employed, and the indifferent electrode was kept well away from both the region of the point stimulated and the area of reference.

OBSERVATIONS

Position of trigger points and reference areas.—The table gives a list of the approximate positions of the trigger points investigated, together with their reference areas. The trigger points appeared to be distributed at random; many were first discovered as a result of scratching or squeezing a small pimple on the skin, and, in general, reference appeared to be more easily obtained from areas of skin which were mildly inflamed. The areas of reference were also distributed at random; in some cases reference occurred to the skin within the territory of the same spinal segment, but in others it appeared in an area

which had no segmental relationship to the trigger point. In no case in this series of observations was the reference of pain found to transgress the mid-line of the body.

Reproducibility.—It was possible to mark out trigger points with the greatest accuracy, and the blindfolded subject could invariably identify them (by the occurrence of reference) with a precision far in excess of the accuracy of localization of even tactile stimuli. Stimulation of the marked spot was effective irrespective of the position of the part; in addition, the trigger point moved with the skin on the underlying tissues.

The trigger points were in most cases of very small size, and stimulation one or two millimetres away was ineffective. In two instances, however, pain referred to a constant area could be produced by the stimulation of any point along a very narrow band of skin. In both (*see* table, Points Nos. 5 and 8) the band in question was less than 2 mm. in width, approximately 1 cm. in length, and lay proximodistally in the forearm. In another case, pain was referred to an identical area by the stimulation of two distinct spots in the thigh, one being distant 10 cm. from the other (*see* table, Points 13 and 14).

The area of reference from any given point or band remained subjectively constant in position, though its exact situation and extent were more difficult to demarcate.

Biopsy.—A small area of skin (approximately 5 mm. square) surrounding the centre of one of the linear trigger points (No. 8) was removed after the local injection of methylene-blue according to the method of Weddell (1941), in order to study the local innervation. Immediately underneath the Indian ink mark indicating the centre of the trigger point a small cutaneous nerve trunk was found, running superficially in the dermis. This trunk gave rise to no branches innervating the area of skin removed. Immediately beneath the epidermis, a fine interweaving network of nerve fibres of varying diameter was seen, giving rise to beaded terminals which in some instances were circumscribed in their distribution. The cutaneous plexus from which this network was derived was not included in the portion of skin removed. No encapsulated endings were seen in the preparation, although the staining was uniform. The nerve trunk was unaccompanied by blood vessels, and indeed no blood vessels of arteriolar size or greater were recognized. No abnormal fibres were detected within the dermal nerve trunk, but there were a number of degenerating and regenerating fibres within the cutaneous plexus. The condition, though less in degree, was reminiscent of that described by Weddell and Glees (1941) in skin taken from the point of the elbow. It appears not unreasonable to assume that the trauma of repeated testing (pin-prick, pinching, etc.) was responsible for this appearance.

Reversal of reference.—In each case detailed in the table a wide region in and around the area of reference was subjected to painful

stimulation in order to find out whether the reference of pain was reversible, i.e. whether stimulation of the area of reference of a given trigger point would cause pain referred back to the neighbourhood of the trigger point itself. In no case could a *directly* reversed relationship between the centre of the area of reference and the trigger point be demonstrated. In one case (Point No. 17), however, painful stimulation of a point 3 cm. from the centre of the area of reference consistently produced pain in an area whose centre was only 1 cm. away from the trigger point; the intensity of the reversed reference was less than that of the original reference. In a further two cases (Points 6 and 10), painful stimulation of a point approximately 2 cm. from the centre of the area of reference led to the occurrence of pain in areas centred 7 cm. and 10 cm. from the respective trigger points.

Extinction of reference.—After prolonged stimulation the referred response became more difficult to elicit, especially if each stimulus was of more than a few seconds duration. Eventually a "refractory phase" supervened, which commonly lasted for a few hours; when pinching was employed it was noted that the onset of this refractory phase often coincided with the appearance of local whealing. In two instances in which pinching was used daily over a period it was found that after nine days in one case and twelve days in the other the referred response could no longer be obtained; in each case there was a palpable induration of the skin in the vicinity of the testing point. These spots were then left alone for some ten days, after which cautious pinching was recommenced. In one case the referred response returned on the eighteenth day, and in the other it was first noticed again on the fourteenth day after disappearance.[1]

Characteristics of the referred pain.—The descriptions of the sensations experienced were in each case in close agreement. The chief sensation in the area of reference was a sharp stinging, of mildly unpleasant quality but low intensity, and difficult to localize accurately to a point in the skin. The stinging appeared to arise in the centre of a roughly circular zone of vague discomfort varying in diameter from about 2 cm. to about 4 cm. The size of the area of reference so defined appeared to be approximately the same, irrespective of the region in which it occurred. Both the stinging pain and the ill-defined discomfort appeared at their maximal intensity immediately after the appropriate point was stimulated, and subsided as soon as the stimulus was removed, leaving behind a sensation, closely resembling itching, which produced a desire to rub the area of reference. After such rubbing, the "itch" sensation gradually disappeared.

[1]A similar phenomenon occurred in another subject, in whom a "hot" metal surface (48° C.) was used as a continuous stimulus for a period of thirty minutes; a small area of erythema was produced, and from this spot no referred response could be produced until twelve days later, when it once more responded to a pinch stimulus.

Reference of other sensations.—A variety of stimuli was applied to several trigger points, including warmth (warm metal cylinder), cold (ice water and ice), touch (No. 2 and No. 4 nylon suture material), pressure (blunt metal rod) and tickle (cotton-wool). In every case no sensation whatever was felt in the reference area until the intensity of the stimulus became such as to produce local pain. Thus, a metal surface applied at a temperature of 45°C. produced no reference, but when the temperature was increased to 48°C., a burning pain was felt locally, accompanied by a stinging sensation in the area of reference.

Provided that pain resulted at the trigger point, it did not seem to matter how that pain was produced. Some methods, however, produced a more prolonged referred response than others. Thus, in one experiment the injection, both intracutaneously and subcutaneously, of 0·4 c.c. of 6 per cent saline in the region of a trigger point on the right forearm produced considerable discomfort in the reference zone for a period of some ten minutes.

Sensory changes in the area of reference.—Prolonged stimulation of the trigger point was found to lead to objectively demonstrable sensory changes in the area of reference. The stimuli were of three kinds: prolonged faradic stimulation, injection of 6 per cent saline, and the application of local heat by means of an electrically heated metal cylinder, 12 mm. in diameter, equipped with a thermocouple measuring the temperature of its surface.

As in the case of the production of referred pain, it was found that no effects could be produced unless the stimulus was adequately painful, and this was particularly noticeable when a heat stimulus was employed.

Approximately ten or fifteen minutes after the application of an effective stimulus to the trigger point it was found that the subject could mark out with considerable accuracy an area of altered sensibility corresponding to the area of subjective reference of pain for that particular trigger point. Gross stimulation of this area, by passing the hand over it, gave rise to a rather unpleasant feeling which was described by one subject as similar to the sensation aroused by stroking the area of reference of pain produced by the injection of hypertonic saline into muscle. Sensory testing by vertically applied pin-prick revealed a well-defined area of hypo-algesia whose borders were reproducible in repeated experiments on the same area. Within this area there were regularly several scattered spots in which a pin-prick was reported as excessively *sharp*; these spots were apparently distributed at random. If the point of the pin was dragged across the area in a continuous stroke, an unpleasant subjective reaction was produced. Nevertheless, when such strokes were compared with similar strokes made on a control area of skin, they were invariably felt as being of lower *intensity* than normal. In a number of experiments lasting over thirty minutes, this condition was present in greater or less degree from about the fifteenth minute onwards, but it did not appear to be progressive. Recovery

within a few minutes usually followed the removal of the actuating stimulus. No unequivocal alteration in touch or thermal sensibility could be demonstrated in these experiments.

Discussion

The observation that a painful stimulus applied to one area of skin is capable of giving rise to pain "referred" to another is not new. As early as 1733, Hales recorded a case of reference from the right knee to the left shoulder-blade; Monro (1895) described a case in which pressure on the dorsum of the right forearm induced pain on the right side of the chest, and later (Monro, 1898) he discussed a number of similar observations. Sherrington (1900) produced in himself pain referred from the skin over the sternum to an oval area above the elbow on each side, and Weir Mitchell (1897), Witmer (1897) and Livingston (1943) note other instances of skin to skin reference. The fullest account of such phenomena is, however, given by de Fromentel (1888), who describes, among many similar instances, reference of pain to the left lumbar region on squeezing an acne pustule over the sternum. He called such pains "synalgias," and noted that the relation between the irritated point and the "sympathetic" point was very constant. He further observed that the sympathetic point was generally on the trunk, and on the same side of the body as the irritated point. He concluded that synalgias "constitute phenomena of a cerebral or psychical order, and result from the action of one perceptive centre upon a neighbouring, intimately related, perceptive centre" (Monro, 1898).

The present findings are in general conformity with the descriptions given by these observers, though contralateral reference has not been seen.

The reference of pain to a poorly localized but circumscribed area of skin, the mildly unpleasant response, and the objectively demonstrable sensory changes in the area of reference all combine to suggest that the process does not differ in any material respect from the process of pain reference from deeper structures (Sinclair, Weddell and Feindel, 1948). It is therefore reasonable to assume that any theory elaborated to account for the reference of pain from deeper tissues should also be applicable to referred pain aroused in the skin.

Sinclair, Weddell and Feindel (1948) have recently suggested that one factor concerned in the production of referred pain is the existence of branching among the axonal pathways conveying the sensation of pain. A painful stimulus applied to one terminal of a branched axon is presumed to arouse, in the branch leading to the area of reference, antidromic impulses, which in turn initiate pain conveying impulses in that area. Such a mechanism could explain most of the findings in the present investigation.

Since the trigger points move with the skin on the underlying tissues, they must lie in the epidermis or dermis, and their punctate

character suggests that the structures responsible are probably not cutaneous pain endings since each pain "net" covers an appreciable area (Weddell, 1945). Histological observations showed a small nerve trunk in immediate relation to one such trigger point and the possibility that stimulation of such nerve trunks is responsible for the reference of pain is strengthened by the observation that in two instances stimulation at any point along a very narrow band of skin gave rise to pain referred to exactly the same position.

Nevertheless, only a very small proportion of the many hundreds of small nerve trunks stimulated in the course of these investigations gave rise to referred pain. The "active" nerve trunks might well be those which contain one branch of a branched axon system whose other terminal lies in the area of reference (Sinclair, Weddell and Feindel, 1948). In the spinal nerves of the frog approximately 0·5 per cent of cutaneous fibres have another cutaneous terminal branch lying in the distribution of the other division of the spinal nerve (Adrian, Cattell and Hoagland, 1931; Hoagland, 1936), but there is no estimate of the frequency of such branched axons in the cutaneous nerves of man.

The ready inactivation, by rough handling, of the "trigger point" may well be due to damage of the specific axon involved; an interval will then elapse before function in the nerve fibre is restored and referred pain can once more be produced.

In three instances stimulation in the region of the area of reference produced pain in the region of the trigger point. If these cases are accepted as direct reversals of reference, the existence of an axon reflex is the simplest explanation available. The fact that the reversed reference is in no case exact is to be expected if the reference of pain in these circumstances depends on the stimulation of a small cutaneous nerve trunk rather than on the stimulation of a pain ending. The reversal of a reference aroused in this way would naturally lead not to the original site of stimulation, but to the region of the terminals of the axon concerned.

It is interesting that pain appears to be the only sensation which can be referred. A chemical mechanism in the periphery has been postulated in the branched axon hypothesis, and the modality of pain is the only one in the arousal of which a chemical factor is known to be implicated (Lewis, 1942). Nevertheless, the speed of the reaction in the present instance argues against the implication of a chemical intermediary.

There remains to be considered the relation between the site of stimulation and the site of reference. In a number of instances both of these lie within the generally accepted compass of a single spinal segment, and it may readily be assumed that a single axon has branches which are distributed to both spots within the territory of that segment. But, as Livingston (1943) has pointed out, stimulation may give rise to sensations in distant areas, and such instances pre-

ponderate in the table—perhaps because they are more readily noticed on account of their very strangeness. All three instances in which "reversal" of the reference process could be demonstrated were of this type. If the branched axon explanation applies to these cases, it follows that the terminals of the branches may lie in the territories of different segments of the spinal cord. It is well known that in the territory of a regenerating peripheral nerve a painful stimulus applied to one point is frequently interpreted as arising from another. The currently accepted explanation of this phenomenon is that the axon stimulated has "lost its way" through being wrongly guided by the various influences responsible for its regeneration (Hawkins, 1948). It appears to be equally reasonable to assume that in the developing embryo a few axons give off branches which find themselves in a similar manner diverted into distant territories, possibly by doubling back into the spinal cord and leaving it again by another route, or possibly by being forced into a prolonged "Odyssey" in a peripheral nerve plexus. This explanation is naturally put forward with the greatest reserve, since there is no direct anatomical evidence as yet for the existence of these pathways, though the observations of Windle (1931) and Barron and Matthews (1934) are perhaps relevant. Nevertheless, none of the current theories regarding the mechanism of referred pain is, as at present enunciated, capable of affording a satisfactory explanation of such cases of distant reference, and the matter is clearly one which merits intensive investigation.

Summary and Conclusions

In the skin of a number of subjects well-defined spots have been found which, when subjected to painful stimulation, "refer" pain to other areas of skin, sometimes to a considerable distance, and even to the territory of a distant spinal segment. This reference of pain may be accompanied by alterations in cutaneous sensibility in the area of reference if the stimulation is prolonged, and the process appears to be essentially similar to the reference of pain to skin from internal organs and deep somatic structures. The phenomena of referred pain may be studied with much greater ease when they are elicited from the body surface, and the study of skin to skin reference may afford much information on the subject of referred pain in general.

It is concluded that the occurrence of referred pain from any tissue (including the skin) to the skin may perhaps be accounted for in part by the explanation advanced by Sinclair, Weddell and Feindel (1948) which depends on the assumption that branching occurs among the sensory pathways conveying the sensation of pain. It is suggested that one limb of a branched axon passes to the site of stimulation, and the other to the area of reference. This mechanism involves the production of secondary pain impulses actually having origin at the periphery. This theory appears to be the best available in the light of current

knowledge, but it is submitted with the greatest caution, for it does not yet rest on a conclusively demonstrated anatomical basis.

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SITE OF "TRIGGER POINTS" AND THEIR RESPECTIVE REFERENCE AREAS

"Trigger Point" Number	*Subject*	*Situation*	*Approximate centre of reference area*
1	D. S.	Radial border of dorsum of right forearm, 16 cm. below olecranon	1 cm. proximal to right olecranon process
2	D. S.	2 cm. above highest point of left iliac crest	Spine of seventh cervical vertebra
3	D. S.	Anterior end of fifth right intercostal space	Mid-way between umbilicus and right anterior superior spine
4	D. S.	Fifth right intercostal space in nipple line	Right groin, 3 cm. medial to anterior superior spine
5	D. S.	Middle of dorsum of right forearm, linear; centre 14 cm. below olecranon	Seventh right intercostal space, half-way between anterior axillary and nipple lines
6	D. S.	Seventh intercostal space, half-way between axillary and nipple lines, distant 2 cm. from the centre of area of reference of point No. 5	Medial border of right forearm, 9 cm. distal to olecranon, and distal 7 cm. from point No. 5
7	C. A. W.	Overlying insertion of right coracobrachialis	Posterior fold of right axilla
8	C. W.	Dorsum of right forearm, linear, centre 12 cm. from lateral epicondyle and 4½ cm. from mid-line	9½ cm. above the line joining the highest points of the iliac crests and 3½ cm. to the right of the mid-line
9	C. W.	Middle of dorsum of left arm, 14 cm. above olecranon process	Ninth left intercostal space in mid-axillary line
10	C. W.	Ninth left intercostal space in mid-axillary line, 2 cm. from approximate centre of area of reference of point No. 9	Lateral wall of left axilla, 10 cm. from point No. 9
11	C. W.	Right arm 14½ cm. below acromion	Ninth right intercostal space in mid-axillary line
12	R. H.	Seventh right intercostal space in anterior axillary line	3 cm. below right thoracic margin in nipple line
13	R. H.	9 cm. above lateral condyle of the right femur	Sixth right intercostal space in anterior axillary line
14	R. H.	Right thigh, 8 cm. above patella, 10 cm. distant from point No. 13	Exactly the same as area of reference of point No. 13
15	R. H.	Right thigh 5 cm. anterior to point No. 13	Eighth right intercostal space in the posterior axillary line
16	R. H.	Medial surface of left thigh, 8 cm. above adductor tubercle	11 cm. from mid-line on left costal margin, mid-way between nipple line and anterior axillary line
17	R. H.	3 cm. below centre of area of reference of point No. 16	1 cm. above point No. 16
18	R. H.	2 cm. lateral to centre of area of reference of point No. 17	3 cm. above medial epicondyle of left humerus

PROGRESSIVE FIBRINOID DEGENERATION OF FIBRILLARY ASTROCYTES ASSOCIATED WITH MENTAL RETARDATION IN A HYDROCEPHALIC INFANT[1]

BY

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In the following case of progressive hydrocephalus in an infant, the brain displays on histological examination a type of degeneration which cannot be identified with any of the forms described in the literature. It is therefore considered worthy of reporting.

Case Report

Clinical history.—J. M., a male aged 15 months, was admitted on October 30, 1947, to the London Hospital on account of an increase in the size of his head, first noted at the age of 7 months. In the month before admission the circumference increased by 2·5 cm. and during this time the child had been fretful, slept poorly, screamed day and night and had been vomiting copiously. At the age of 8 months it was first noticed that he was backward as he was neither sitting up nor attempting to do so. At the time of admission he still could not sit up or raise his head.

The birth-weight was 2·41 kilos. He was delivered by Cæsarian section at the eighth month because of placenta prævia.

On examination.—A fretful, backward child, who could not sit or raise its head. Physical development was less than normal for its age.

The skull had a circumference of 50 cm., the frontal region being unduly prominent. The anterior fontanelle bulged even when the child was not crying. The central nervous system showed no abnormality. The plantar responses were extensor on both sides. The other systems were normal.

A lumbar puncture seventeen days before death yielded approximately 1 c.c. of water-clear fluid. Cells were less than 5 per c.mm. Protein 30 mg. per 100 c.c. W.R. negative. Lange 011100.

Progress.—On the day after admission the child developed a fever which continued without remission until death three weeks later. Re-examination after a few days showed no further signs except an increased respiratory rate, tachycardia and fever, with doubtful signs at the right base. The child was more irritable. Chemotherapy with penicillin and sulphamethazine failed to influence the temperature. Eleven days before death a Jacksonian seizure occurred involving the right side, with twitching of the mouth and eye and movement of the arm and leg. This was followed by a period of coma lasting five minutes. Diarrhœa and vomiting began and became severe. A rectal swab yielded no pathogenic organisms. The child gradually became more dehydrated, the temperature rose still further and he became comatose. Death occurred in hyperpyrexia on November 19, 1947.

Family history.—Both mother and father are alive and well. One sib died fifteen days after delivery, presumably following birth trauma in an extended breech presentation. The second child, a girl now aged 4 years 3 months, has never been seriously ill, is described as intelligent and observant, and is at present quite healthy.

[1]Carried out during the tenure of a Nuffield Foundation Fellowship.

There is no consanguinity between husband and wife, and no known nervous disease in any member of the family on either side.

The pregnancy was normal as far as the mother's health was concerned. Two episodes of hæmorrhage at 3 and 6 months were treated conservatively, and severe hæmorrhage at the seventh month was followed by Cæsarian section for placenta prævia. The parents report noticing a small area of abrasion on the right side of the head, when the child was brought home at the age of 6 weeks.

Pathological Examination

Necropsy was performed eight hours after death.

Summary (P.M. 386. 1947).—*Pulmonary Embolism; Recent thrombosis of left lateral sinus; Internal hydrocephalus.*

A poorly nourished male child (length 74 cm.; weight 6·52 kilos). The head measured 50 cm. in circumference. Anterior fontanelle 5·5 by 4·5 cm. Cerebral hemispheres full and symmetrical. No visible abnormality on external surface of brain. Red and purple ante-mortem thrombus firmly adherent to wall throughout left lateral sinus, and extending into junction of this with straight sinus. No gross evidence of organization of the clot. Superior longitudinal sinus continuous with right lateral sinus; these and all other dural venous sinuses contained purple gelatinous post-mortem thrombus.

Occlusion by ante-mortem clot of branches of pulmonary artery to right and left lower lobes. Slight congestion of lungs. Mucopus in trachea and main bronchi. Fatty liver. No abnormal changes found in remaining organs.

Brain weight 1,210 grammes (normal at 18 months 1,042 grammes).

Examination of brain after fixation.—The leptomeninges appeared normal, the arachnoid over the cisterna magna being quite transparent. The cerebral convexities were full and symmetrical. The foramen of Magendie was widely patent, measuring 0·4 cm. diam., and the aqueduct was slightly enlarged, measuring 0·3 by 0·2 cm. in coronal section between the anterior and posterior corpora quadrigemina. The third ventricle was small. The cavum septi pellucidi was greatly expanded measuring up to 2·5 cm. transversely, 2·5 cm. vertically and 4·3 cm. antero-posteriorly. Its walls were smooth, bulging into each lateral ventricle and apparently compressing the foramina of Monro (each 0·2 cm. diam.) (fig. 1). Both lateral ventricles were moderately dilated. There were greyish discoloration and slight softening of the white matter about both frontal horns, in the corona radiata, and extending diffusely towards the orbital surfaces of the frontal lobes. The ependyma throughout the lateral ventricles was smooth, grey and glistening. The subependymal tissue was tough and rubbery on palpation.

Microscopical examination.—The lung shows some macrophages with foamy cytoplasm in the lumen of the bronchi. The liver shows a fatty change throughout the parenchyma. Discrete groups of these cells, often periportal, have a finely foamy cytoplasm and shrunken pyknotic nuclei. In frozen sections most of the fat is brightly sudano-

phil and isotropic. The groups of foamy cells contain little sudanophil material in the form of minute granules; their unstained content is doubly refractive, yielding maltese crosses on the application of heat. The Kupffer cells appear normal. The kidneys and pituitary gland are normal.

Representative blocks of the *central nervous system* were embedded in paraffin wax, neighbouring blocks of several of these were cut on the freezing microtome. Sections were stained by a wide range of methods including numerous silver techniques.

The most striking feature of the histology of the central nervous system is the presence, in all the sections examined, of large numbers of homogeneous bodies which take the form of elongated rods, up to about 30 μ, with tapered, rounded or blunt ends. They are arranged radially around the walls of blood vessels (fig. 2) or perpendicularly to the surface of the brain in the subpial zone. They are also evenly disseminated throughout the brain where they are smaller, sparser and generally shorter, of variable shape and size, corresponding approximately to the size of a red blood corpuscle (fig. 2).

Staining reactions of the bodies.—With hæmatoxylin-eosin they stain a light bluish-pink, distinctly different from the red blood corpuscles. They are bright red with Lendrum's phloxine-tartrazine stain. With van Gieson they stain bright yellow, in Mallory's phosphotungstic-acid hæmatoxylin bluish-purple. With Heidenhain's azan, they vary from blue to red. They stain intensely blue in Anderson's victoria blue method. They are brilliantly and uniformly fuchsinophil in Alzheimer's light green-acid fuchsin stain for neuroglia. They have a strong affinity for hæmatoxylin in Loyez' myelin-sheath stain, staining jet black. They have no affinity for the hæmatoxylin, however, in Spielmeyer's method for myelin sheaths. They do not stain for lipoids with Sudan III, osmic acid or Nile blue sulphate. They appear in paraffin sections, having resisted solution in alcohol and chloroform. They are insoluble in ether. Some of the material examined had been fixed for many months in formalin; this, however, had no effect upon their histological appearances.

They do not stain for amyloid with crystal violet, nor do they give a metachromatic reaction with toluidine blue or thionin in either paraffin or frozen sections. They give no reaction for mucin with mucicarmine. They stain moderately well, but variably, in the various silver impregnations. The Feulgen reaction for nucleoproteins and the von Kossa reaction for calcium are both negative. No reaction for iron is given either by the Prussian blue or by Turnbull's blue method.

The distribution of the bodies.—In the cerebral hemispheres they are to be seen especially in a zone of variable depth beneath the ependyma, and here they are much more closely packed around the blood-vessels than in the intervening tissue. In the white matter they are present both as perivascular cuffs and scattered diffusely through the

fibre tracts. They diminish gradually in numbers as one proceeds from the peri-ependymal tissues to the subarcuate fibres, and are not visible, as a rule, in the white matter of the gyri. They are absent from all parts of the cortex examined. In the marginal layer, a further collection is found immediately beneath the pia mater, and surrounding some of the vessels entering the substance of the brain.

Slight variations in distribution are found in different parts of the hemisphere. Thus in the occipital lobe the subpial collection is generally absent except in the depths of the sulci, while in the frontal and parietal lobes the subpial zone is filled continuously. In the left gyrus rectus the white matter is affected as far as the tip of gyrus, but the subpial zone is discontinuous, and is limited to the depths of the sulci. In the basal ganglia, the peri-ependymal tissues of the walls of the third ventricle are affected, again with accentuated perivascular distribution but the nuclear masses themselves contain very few bodies. The fibre tracts of the internal capsule have sparsely scattered bodies between the bundles.

In the brain-stem, the distribution from the mid-brain down to the lower medulla (the lowest portion available for examination) is essentially similar. A dense subpial zone extends around the whole circumference of the brain-stem, throughout its whole length (fig. 4). The subependymal tissues do not contain any of these bodies, but a cuff surrounds the vessels near the aqueduct. The bodies are scattered diffusely through the tracts and nuclei of the brain-stem with concentrations around the vessels. In the cerebellar hemispheres the white matter shows a sparse distribution of the bodies. The cerebellar cortex is entirely free from them and in the subpial zone there are very few small collections. They are found in the superior medullary velum. The only portions of nerve trunk available for examination consisted of cranial nerves attached to the brain-stem and medulla. The third, fourth, eighth, and a rootlet of the ninth, cranial nerves all contain collections of these bodies beneath their pial covering. In the ninth nerve the glial outgrowth into the rootlet is surrounded by a frill of swollen glial processes identical with the bodies noted above (fig. 5) while beyond the margin of the glial extension no sign of these structures can be seen and the nerve itself is normal.

The histological findings may best be described by dissociating the elements of the nervous system and summarizing the changes found in each of these elements in all the sections.

(1) *Nerve cells, nerve fibres and myelin sheaths.*—Spielmeyer and Loyez hæmatoxylin preparations of cerebrum, mid-brain, and medulla oblongata, show clearly that demyelination is not an important feature of this disease. In the cerebral hemispheres, the white matter may be described in four zones. A zone beneath the ependyma contains no myelin sheaths or nerve fibres; it is in this zone that the gliosis is most marked and the bodies are in greatest numbers. In a broader zone

outside this, the myelin sheaths are compactly arranged and deeply stained, and the bodies are fewer. Between this zone and the subarcuate fibres, which are also well preserved, a mid-zone of pallor is seen (fig. 6). The myelin sheaths are less compactly arranged, they vary in their staining and many of them are beaded. The nerve fibres in this zone of pallor stain poorly and are separated by large numbers of bodies, but there is no evidence that this association is pathogenetically significant and there is no axonal degeneration.

The pyramidal cells of the cerebral cortex show only acute cell changes which are probably the result of hyperpyrexia and of post-mortem degeneration. The nerve cells of the substantia nigra are in stages of advanced chromatolysis. The nuclei of the reticular substance of the pons and the peri-aqueductal nuclei also stain poorly, and the dentate nucleus shows similar acute changes.

The relationship of the bodies to the trunks of the cranial nerves is referred to above.

(2) *The neuroglia.*—(*a*) *Oligodendroglia*: In the descending fibre tracts of the brain-stem the oligodendroglial cells are not numerically reduced but show quite well marked acute swelling. In the subependymal zone no oligodendroglia can be recognized while in the adjacent normally myelinated zone these cells are reduced in number and show advanced acute swelling. They increase numerically as the cortex is approached, with reduction in the degree of acute swelling. Some of the oligodendroglial cells in the cortex display normal processes in Penfield preparations. The numbers of the oligodendroglia are most nearly normal in the white matter of the gyri.

(*b*) *Astrocytes:* These cells stain irregularly and with difficulty. The silver methods by which they were best impregnated were the Bielschowsky, Weil-Davenport, and Hortega's double impregnation methods. Degenerative and proliferative changes are seen in the astrocytes. Proliferation has led to the formation of focal collections of hypertrophied fibrillary astrocytes throughout the brain. These collections are found most frequently in the subpial, subependymal and perivascular situations, although occasionally they are found in areas of white matter apart from these. The astrocytes have long, irregular, tortuous and swollen processes which, in the marginal layer of the cortex, run into the subpial zone of bodies. The cerebral cortex is not involved but some nuclear masses in the brain-stem, especially the substantia nigra, show gliosis. Thus the distribution of this form of astrocyte reaction approximates to that of the greatest concentration of these bodies; on the other hand, in many areas, especially the subpial, no astrocytes are to be seen near quite large collections of the bodies.

In that part of central white matter of the cerebrum which stains poorly for myelin sheaths, the astrocytes show a severe degenerative change and in their general morphology they recall the "amœboid

glia" of Alzheimer. The nuclei are pyknotic and eccentric, the cytoplasm is swollen and eosinophilic with rounded or undulating margins and no processes are visible (fig. 7).

In Alzheimer's light green acid fuchsin preparations, and in some of the silver stains, typical "bodies" are found in the cytoplasm of these astrocytes. The bodies stain red in the Alzheimer stain against the green cytoplasm of the cells. In addition the "amœboid" cells contain minute spherical fuchsinophil granules. Occasional astrocytes are shrunken and are diffusely and densely fuchsinophil. Moreover in this stain the fine neuroglial fibres can often be traced into fusiform or nummular swellings which present all gradations to the typical "bodies" (fig. 4). Fragmented neuroglial fibrils in the nervous tissue remote from vessels or pia show similar moniliform swellings which morphologically bear a superficial resemblance to "asbestosis bodies."

Thus despite the occurrence of the "bodies" in areas where astrocytes are not stained, the morphology of the astrocytes in specific preparations provides definite evidence that these "bodies" have resulted from degeneration of these cells and their processes.

(3) *Microglia.*—Using Penfield's modification of Hortega's silver carbonate method and Weil-Davenport's ammoniacal silver method, no increase in microglia is found in the cerebral hemispheres. Only an occasional microglial cell is seen in a perivascular space. These do not show the characters of compound granular corpuscles. In the midbrain, however, the substantia nigra shows a dense microgliosis and is infiltrated with large numbers of cells in early amœboid phases (fig. 8). No lipoids are present in these cells in sections stained with Sudan III.

Summary of Pathological Findings

The cause of death in this infant was massive pulmonary embolus arising from the left lateral sinus. The thrombosis of the cerebral venous sinuses is secondary to the marasmus and inanition produced by a progressive cerebral degeneration associated with hydrocephalus. Microscopically this cerebral degeneration is remarkable for the presence of large numbers of rod-shaped, rounded or nummular bodies in the white matter and in the subpial zone of the marginal layer of the cortex. They have the staining reactions of fibrin but, apart from this, histochemical studies do not offer any clear indication of their chemical structure. Their distribution, arrangement and morphological relationships to the fibrillary neuroglia collectively indicate their origin from the fibres or fibrillary processes of these cells. There is patchy gliosis throughout the hemispheres and brain-stem. The cerebral and cerebellar cortices appear normal but nuclear masses in the brain-stem stain poorly and are the sites of considerable astrogliosis and microgliosis. Demyelination is not a feature.

Discussion

This case presented clinically as one of mental retardation first noticed eight months after birth. From this time onward the child's mental state remained stationary but there was a progressive increase in the size of his head. During the month before admission signs of raised intracranial pressure appeared with more dramatic symptoms. This terminal illness was complicated by hyperpyrexia, diarrhœa and vomiting and by dehydration.

There is no evidence to suggest any familial basis for the disease. It does not seem to have been congenital.

The physical signs indicated a diffuse rather than a localized cerebral lesion although a single Jacksonian seizure on the right side did occur.

The increase in circumference of the skull and especially the rapid increase measured in the month before admission pointed to a diagnosis of hydrocephalus. The pathological explanation for this hydrocephalus is uncertain. Gross dilatation of the cavum septi pellucidi is the most striking observation. It is possible that this dilatation is partly responsible for the increase in size of the head. The lateral ventricles are also dilated and this may be due to occlusion of the foramina of Monro by the dilated cavum. There is gross subependymal gliosis around the lateral ventricles which might lead to some *evacuo* dilatation. No atrophy of the brain was apparent either by weight or inspection, and there is no evidence of any meningitis which might have occluded the basal cisterns. The third and fourth ventricles are not dilated. Thus the increase in size of the head is explained by the dilatation of the cavum for which no reason can be given, and by the dilatation of the lateral ventricles due either to occlusion of the foramina of Monro or to gliosis of the subependymal tissues, or both.

The histological changes found in this case appear to be unique. No published record of a similar case has been found. The primary pathological change would seem to involve the fibrillary astrocytes. Some of these cells show a chronic progressive reaction with the formation of focal collections of hypertrophied fibrillary neuroglia, while others show a severe degenerative change resulting in typical "amœboid glia." It is this degenerative change that appears particularly to be related to the production of the fibrinoid bodies. Several items of evidence support this view. First, the distribution of the bodies in this case corresponds closely to that of the fibrillary astrocytes. Thus they are absent from the cortex, but are predominantly found in the subpial, subependymal and perivascular situations previously described. In the basal nuclei they are very sparse. On the other hand their distribution is quite different from that of other structures which might be implicated. The oligodendroglia are not usually present in the subependymal and subpial zones but they are present in the cortex which here is unaffected. The myelin sheaths, having the same distribution,

are similarly excluded and the myelin sheath stains do not suggest any extensive destruction.

Secondly, the staining reactions of the bodies are, in general, similar to those of glial fibres. At the same time they give many of the reactions of fibrin. Since it is considered that they are a degeneration product, the term "fibrinoid" is applied to them on the basis of these staining reactions. In several of the preparations as described above, notably in Alzheimer's light green acid fuchsin method, the fibrinoid bodies could be demonstrated in the cytoplasm of the astrocytes, and their close relation to the astrocyte fibres determined.

Thirdly, it is common to find similar bodies in the astrocytomas, especially the fibrillary type occurring in the third ventricle and cerebellum in children.

The oligodendroglia show various stages of acute swelling as is to be expected in any post-mortem examination of the brain. Although in some areas they are reduced in numbers, there is no direct evidence which implicates them in the formation of the bodies. The distribution of these cells is also quite different from that of the bodies.

The nerve cells show changes which may be attributed to post-mortem degeneration and to the terminal hyperpyrexia. No evidence of neuronophagia is seen, which also suggests that the neuronal changes are the result of some terminal process. In the substantia nigra, however, a microglial reaction in the surrounding tissues and the advanced chromatolysis of the neurones suggest that the process may be of longer standing.

The ætiology of the disease remains obscure. No evidence of an inflammatory process was found. There were no significant or explanatory changes in the other organs of the body. The focal development of foam-cells containing a doubly refractive, unidentified lipin in the liver parenchyma is of interest. But there was no macroscopic evidence of a similar change in other organs, and certainly no evidence of any disturbance of lipoid metabolism in the brain. It is unlikely that the hydrocephalus is primary since the degree of ventricular dilatation is comparatively slight, and glial changes of this character do not usually complicate internal hydrocephalus. The bodies are also found in the brain-stem where no hydrocephalic distension exists.

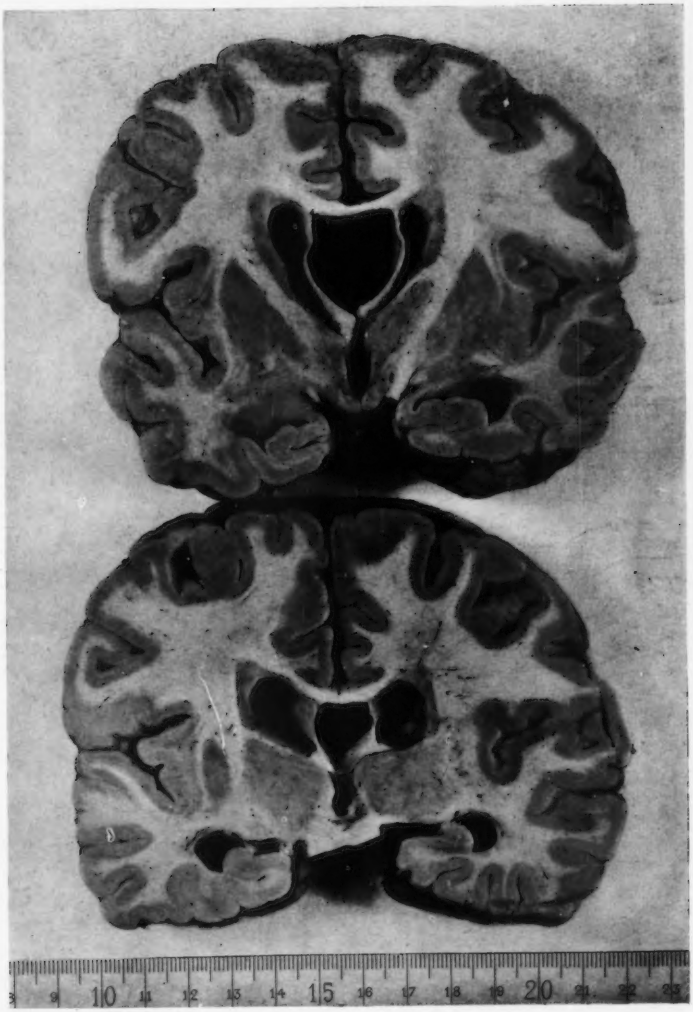
The conclusion is therefore reached that this is a non-familial idiopathic cerebral sclerosis in which fibrinoid degeneration of fibrillary astrocytes has occurred. The clinical equivalent is a severe mental retardation. Hydrocephalus is an associated feature in this case.

Summary

(1) The history and clinical findings are given of a case of mental retardation in an infant with hydrocephalus.

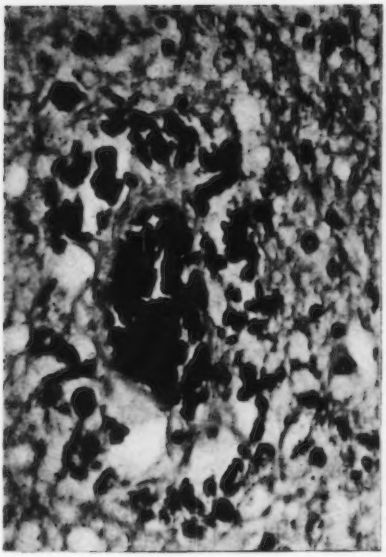
(2) Histological examination of the central nervous system revealed

PLATE XIV.



To illustrate article by W. Stewart Alexander.

PLATE XV.



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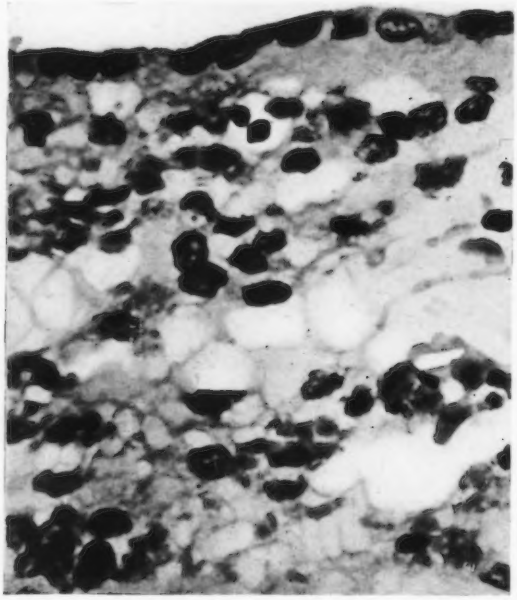

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PLATE XVI.

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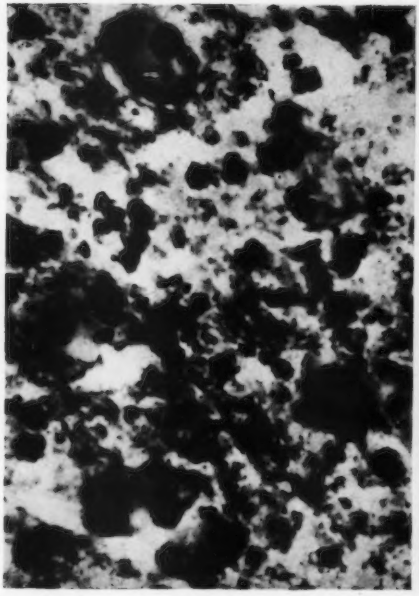

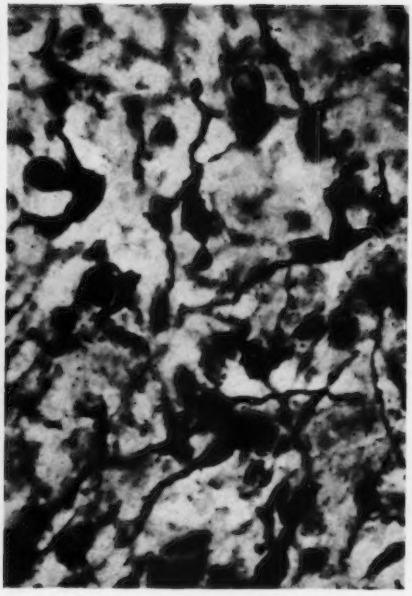

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To illustrate article by W. Stewart Alexander.

the presence of large numbers of fuchsinophil bodies in the white matter and beneath both the ependyma and the pia, but sparing the cortex. They show a characteristic perivascular predominance.

(3) Evidence is presented to show that these bodies are the result of fibrinoid degeneration in the fibres and cell bodies of the fibrillary neuroglia.

ACKNOWLEDGMENTS

I wish to thank Professor Dorothy Russell for valuable assistance and helpful criticism in the preparation of this paper. Mr. John King prepared the photomicrographs.

LEGENDS FOR PLATES

FIG. 1.—Coronal sections of brain showing dilated cavum septi pellucidi and zone of greyish discoloration beneath the ependyma of both lateral ventricles.

FIG. 2.—Perivascular collection of bodies around a small vessel from the deep white matter. Mallory's phosphotungstic acid hæmatoxylin. × 375.

FIG. 3.—Subependymal zone from lateral ventricle. Large numbers of bodies scattered through white matter, smaller than the nuclei and staining less intensely. Hæmatoxylin and eosin. × 700.

FIG. 4.—Subpial zone in the dorsal cleft of medulla showing parallel oricutation of rod-shaped bodies to surface. Alzheimer's acid fuchsin light green method. × 470.

FIG. 5.—Rootlet of ninth nerve showing extension of glia into nerve trunk and a frill of bodies at the margins of the extension. Van Gieson. × 150.

FIG. 6.—Frontal lobe showing four zones—absence of myelin beneath ependyma, mid-zone of pallor between subarcuate fibres and the radiation. Spielmeyer myelin sheath stain. × 2·5.

FIG. 7.—Bodies of astrocytes showing "amœboid" change from white matter of frontal lobe. Hortega's double impregnation. × 750.

FIG. 8.—Microglial cells from substantia nigra in early amœboid phase. Penfield modification of Hortega's silver carbonate. × 645.

SUBACUTE COMBINED DEGENERATION OF THE CORD: I. RESPONSE TO LIVER EXTRACTS. II. TRIALS WITH VITAMIN B_{12}

APPENDIX: QUANTITATIVE METHOD OF ASSESSING NEUROLOGICAL STATUS

BY

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(With Statistical Advice by H. Campbell, Nuffield Department of Industrial Health, The Medical School, Newcastle upon Tyne.)

INTRODUCTION

OBSERVATIONS on subacute combined degeneration of the cord, begun in 1928, first indicated the presence in liver of a factor necessary for the integrity of the nervous system in pernicious anæmia. For the next twenty years efforts to identify this factor were hampered by the slow progress of purification of liver extract. A year ago this difficulty was resolved.

Meanwhile a quantitative method for assessing neurological improvement had been developed. This is described in the Appendix.

Part I describes the effect of liver extracts in 44 cases, a basis for comparison in subsequent trials.

Part II reviews efforts to identify the active principle terminating in trials with Lester Smith's red crystalline anti-pernicious anæmia factor, now known to be identical with vitamin B_{12}.

PART I.—RESPONSE TO LIVER EXTRACTS

The patients in this series were treated during the period 1932–1939. The results indicate the nature of the improvement and elucidate some factors influencing the response.

METHODS

Selection of cases.—Patients selected for trial had clear evidence of subacute combined degeneration with paræsthesiæ, ataxia, Rombergism, inco-ordination of the limbs and impairment or absence of vibration sense. More than half the patients had "extensor" plantar responses. Other findings referable to involvement of posterior or lateral columns were also present. Patients with only minor involvement of the nervous system (e.g. paræsthesiæ with loss of vibration sense and absence of deep reflexes) were excluded.

Cerebrospinal fluid was normal in the few patients who underwent lumbar puncture. Patients with complications such as diabetes or syphilis which might conceivably have contributed to the neurological involvement were excluded. On the other hand, patients with arteriosclerosis, hypertension or minor infections were not excluded; improvement occurred despite these complications (*see* p. 398). Several

cases were rejected because mental changes prevented proper evaluation of subjective data.

Other clinical and laboratory findings were compatible with the diagnosis of pernicious anæmia. All patients had histamine-refractory achlorhydria. One patient had no actual anæmia at any time, although other clinical findings, including glossitis, left the diagnosis in no doubt. The remaining patients showed, or had shown at one period of their illness, the usual hæmatological findings of pernicious anæmia. Marrow examinations—a routine in later cases of this series—showed megaloblastic erythropoiesis accompanied by giant metamyelocytes. Furthermore, all patients responded well to liver therapy.

Diet.—Dietary restrictions were imposed to limit the intake of possible extraneous therapeutic agents, particularly sources of anti-pernicious anæmia factors in food. Vitamin concentrates or other preparations, apart from the material under test, were not given. Some earlier patients in this series (but not those in the Part II series) received chicken once or twice a week. The others had no meat or meat products and no eggs. The diet consisted of white or National bread, porridge or processed cereals, white fish, vegetables, butter, margarine, cheese, sugar and 1 pint of milk daily. On this regime patients very seldom develop a "spontaneous" reticulocytosis or rise of red blood cells. These restrictions, which of course are unnecessary for routine purposes, were removed when the patients left hospital or as soon afterwards as the findings warranted.

Controls.—The natural course of the untreated disease could often be inferred from the patient's history or from previous records. A follow-up of 31 patients admitted to this hospital in the two years prior to the introduction of liver therapy showed that 28 died within two years (average period 14·6 months) from the onset of the disease and the remaining 3 were worse (Ungley and Suzman, 1929*a* and 1929*b*).

Since untreated subacute combined degeneration may relapse suddenly and is, at best, only partly reversible, it was obviously not justifiable to have untreated controls in the present series. For the same reason control periods seldom exceeded ten days. Exceptions include 5 patients described in Part II whose anæmia was kept in check by repeated blood transfusions. In 3 there was improvement in paræsthesiæ, otherwise none improved and 1 became much worse.

Judging from these observations and others in the literature, spontaneous remission of neurological symptoms seems to be rare and for the most part confined to fluctuations in the degree and extent of paræsthesiæ.

Quantitative assessment of neurological status.—The aim of the method (*see* Appendix) was to provide a yardstick for comparing improvement in an individual patient or between groups of patients.

Since most of the symptoms and signs selected were not amenable to direct numerical evaluation, grades were established from the slightest (Grade 1) to the most severe manifestation (Grade 10). This is not to imply that Grade 8 is twice as severe as Grade 4, but merely that a number of distinct intervening gradations are possible.

While no greater accuracy is attained by substituting, say the numeral 1 for "slight", giving each grade a corresponding score did enable us to determine the average grade for a particular symptom in a group of patients and thereby to follow the rate of improvement of this symptom.

Further, after each examination we could obtain a simple expression for the degree of neurological involvement of that patient by adding the scores for individual symptoms and signs. A high total score indicated severe and extensive neurological involvement and a reduction in score meant improvement.

Although the selected symptoms and signs were obviously not all of equal importance, consideration of the pattern of involvement in cases of varying severity and at different stages of treatment (p. 392) showed the use of total scores to be

justified if confined to (*a*) comparison between scores by the same patient at different times and (*b*) comparison between groups of patients.

Material

The 44 cases comprise two groups : 28 received "crude" liver extracts (Campolon in 22, Pernæmon Forte in 6) and 16 an extract of the Dakin and West type (Anahæmin) which is termed "refined."

During the first six months the average weekly dose of crude liver extracts was 20 ml. and of the refined 5 ml. The average maintenance dose thereafter was 8 to 12 ml. of the crude liver extracts or 2 ml. of the refined (*see also* p. 401).

There were 30 males and 14 females with ages ranging from 28 to 78 years (mean 51 years).

Table I.—Mean Values of Observations*

	Crude (28 *cases*)	*Refined* (16 *cases*)	*Total* (44 *cases*)
Age on admission (years) ..	50·2 ± 1·7	52·6 ± 2·5	51·1 ± 1·4
R.B.C. count on admission (millions)	2·92 ± 0·21	2·82 ± 0·26	2·88 ± 0·16
R.B.C. count at six months (millions)	5·31 ± 0·10	5·20 ± 0·13	5·27 ± 0·08
Duration of difficulty in walking (months)	20·3 ± 4·7	13·7 ± 4·4	17·9 ± 3·4
Initial score	70·0 ± 4·4	67·6 ± 5·5	69·2 ± 3·5
Score after six months	38·5 ± 5·4	36·3 ± 6·1	37·7 ± 3·9
Improvement in score (per cent)	44·4 ± 4·3	48·7 ± 5·7	46·0 ± 3·4

*Arithmetic mean ± standard error of the mean.

Red blood cell counts at the commencement of treatment ranged from 1·03 to 5·02 millions (fig. 11), the average being 2·88 millions. Variations in severity are reflected in the total scores, which ranged from 35 to 114 (mean 69). The duration of difficulty in walking ranged from one month to eight years. The high average (eighteen months) is due to the inclusion of a few cases of long standing. The difference between the mean duration of the "crude" and "refined" groups (twenty compared with fourteen months) is not significant, because of the very wide scatter within the individual groups. The two groups were similar in respect to age, sex, severity and degree of anæmia (Table I).

Results

There was no statistically significant difference between the effects of the "crude" and the "refined" liver extracts (Table I). Fig. 1 shows how closely parallel were the rates of improvement. Henceforth the 44 cases will be considered as one group.

The findings will be considered under three headings.

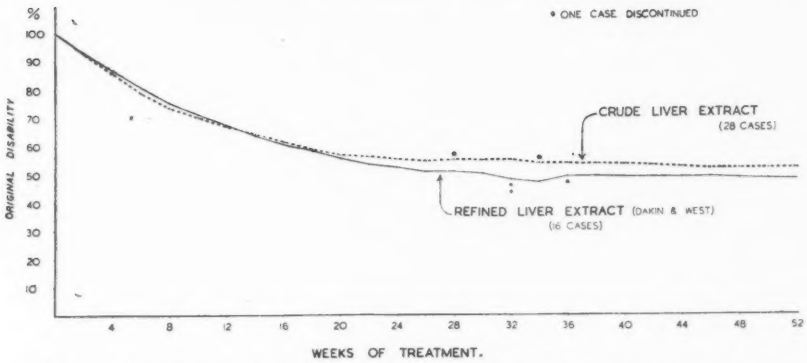

FIG. 1.—Comparison of the effects of crude and refined liver extracts in subacute combined degeneration of the cord. To facilitate comparison the mean total scores for each group are expressed as a percentage of original disability.

A.—EFFECT OF TREATMENT ON INDIVIDUAL SYMPTOMS AND SIGNS

A fixed period of six months will be used for comparing the effects of treatment on the various symptoms and signs. As noted elsewhere (p. 393), 95 per cent of the improvement occurs within this time.

Changes in the mean scores are shown in figs. 5 and 6. In the text the equivalent of these scores, to the nearest digit, is stated in terms of dysfunction.

All patients had *difficulty in walking*. 5 regained normal ability to walk, 35 improved, and 4 were unchanged. The degree of improvement of individual cases is shown in fig. 2. The reduction in mean

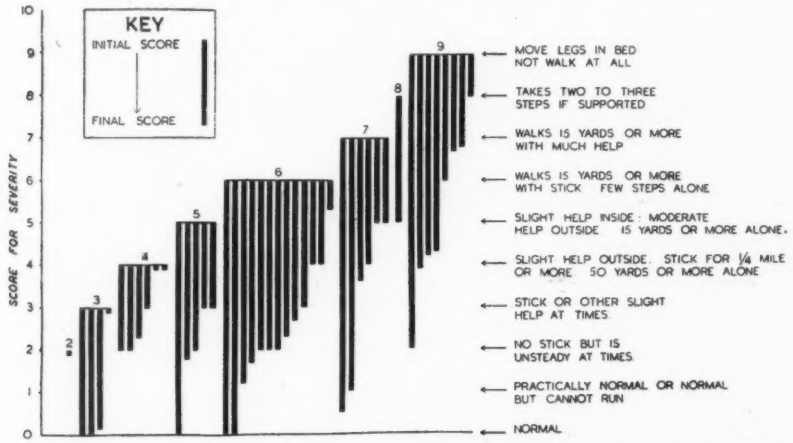

FIG. 2.—The range of improvement of difficulty in walking in 44 cases. Each line begins above with the initial score and ends below with the final score. The length of the line represents the amount of improvement.

score for 44 cases corresponds to improvement from ability to take only a few steps without help to walking long distances alone, occasionally using a stick.

All patients had an abnormal *gait*, which became normal in 9 and improved in 35. The reduction in mean score was equivalent to a change from inability to walk unaided for more than a few steps to walking alone but not without mistakes on a 7·5 cm. line.

All patients showed a positive *Romberg's sign* or were unable to stand. Standing became normal in 14 cases and improved in 30 cases (fig. 3). The reduction in the mean score corresponds to a change from overbalancing in 0 to 5 seconds to some sway but no overbalancing.

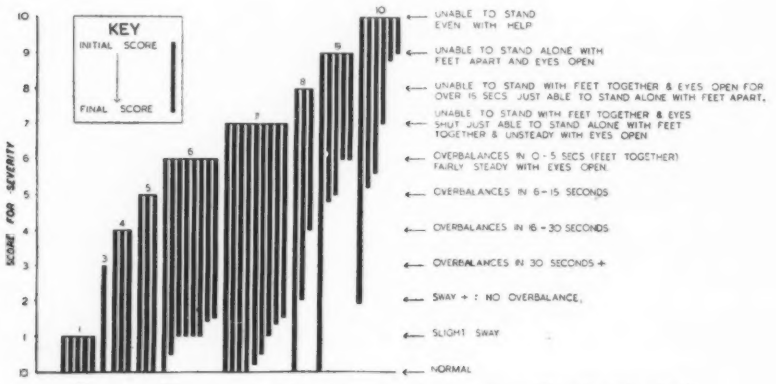
KEY
INITIAL SCORE
FINAL SCORE
SCORE FOR SEVERITY
UNABLE TO STAND EVEN WITH HELP
UNABLE TO STAND ALONE WITH FEET APART AND EYES OPEN
UNABLE TO STAND WITH FEET TOGETHER & EYES OPEN FOR OVER 15 SECS JUST ABLE TO STAND ALONE WITH FEET APART.
UNABLE TO STAND WITH FEET TOGETHER & EYES SHUT JUST ABLE TO STAND ALONE WITH FEET TOGETHER & UNSTEADY WITH EYES OPEN
OVERBALANCES IN 0 - 5 SECS (FEET TOGETHER) FAIRLY STEADY WITH EYES OPEN.
OVERBALANCES IN 6 - 15 SECONDS
OVERBALANCES IN 16 - 30 SECONDS
OVERBALANCES IN 30 SECONDS +
SWAY + : NO OVERBALANCE.
SLIGHT SWAY
NORMAL

FIG. 3.—The range of improvement in standing (Romberg's sign).

Difficulty in using the hands, present in 23 patients, disappeared in 14 cases, improved in 7 and was unchanged in 2 (fig. 4). The reduction in mean score (fig. 5) corresponds to a change from "movements clumsy, unable to knit or sew, writing poor, difficulty with small buttons" to a slight defect in the finer movements of one hand.

Recognition of objects placed in the hand, impaired in 10 patients, became normal in 5, improved in 3, was unchanged in 1 and temporarily abnormal in 1.

Paræsthesiæ in the upper limbs, noted in 36 patients, disappeared in 11, improved in 14, were unchanged in 3, appeared temporarily in 2 and became worse in 6 cases. The reduction in mean score was equivalent to a shrinkage of the level of paræsthesiæ from the base to the distal half of the fingers.

All patients had paræsthesiæ in the lower limbs, often extending on to the trunk. Paræsthesiæ ceased in 6, improved in 22, were unchanged in 11 and became worse in 5 cases. The reduction in mean score was equivalent to a shrinkage in the level of paræsthesiæ from the knees to the ankles.

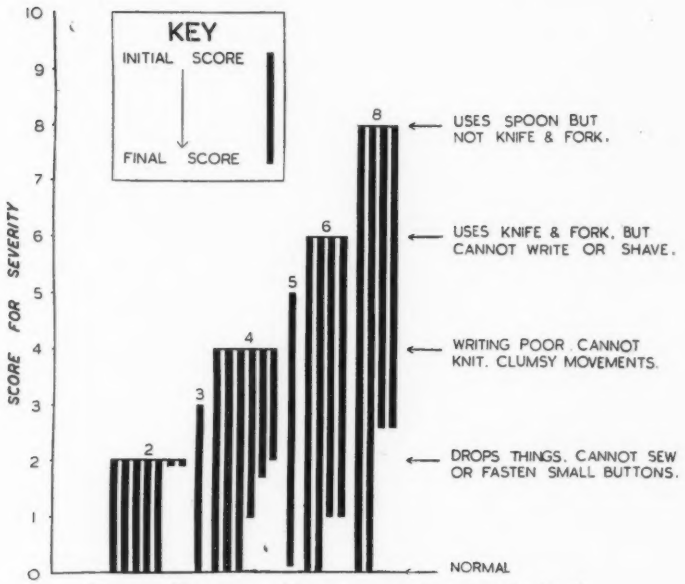

FIG. 4.—The range of improvement in using the hands.

Co-ordination of the upper limbs, defective in 17 patients, became normal in 8 cases, improved in 5, was unchanged in 3 and worse in 1.

Co-ordination of the lower limbs, defective in all patients, became normal in 4, improved in 36, was unchanged in 2 and worse in 2 cases. The reduction in mean score was equivalent to a change from a moderately severe to a slight defect.

Joint sense in the fingers, defective in 14 patients, became normal in 7, improved in 4, became temporarily abnormal in 1 and worse in 2.

Joint sense in the toes, defective in 42 patients, became normal in 8, improved in 21, was unchanged in 9, temporarily abnormal in 1 and worse in 3 cases.

It was not possible in all patients to determine a definite level of loss of *vibration sense*. As judged by tests confined to the shins and malleoli, 4 cases became normal, 1 improved, 37 were unchanged and 2 were worse.

In 20 patients, however, a definite level of loss could be ascertained. Assessed on this basis the average initial score for these patients corresponded to a level of loss extending up to and including the sacrum. Vibration sense became normal in 4, improved in 4 and was unchanged in 12. After six months the average score was equivalent to absolute loss in malleoli, shins and patellæ, and partial loss in the anterior superior iliac spines.

The 20 cases chosen for this assessment of vibration sense were a

representative sample of the 44 cases in respect to severity (mean initial score 72·6 ± 8·5), duration of difficulty in walking (mean 17·2 ± 3·3 months), degree of anæmia (mean initial red blood cell count 2·82 ± 0·25 millions per c.mm.) and degree of neurological improvement (mean percentage reduction in total score 48·9 ± 5·8).

Sensation to touch and pin-prick in the hands, defective in 43 patients, became normal in 9, improved in 3, became temporarily abnormal in 4 and worse in 1. The reduction in the mean score corresponds to an almost complete disappearance of hypoæsthesia in the distal half of the fingers.

Sensation to touch and pin-prick in the lower limbs, defective in 43 patients, became normal in 3, improved in 23, was unchanged in 9 and worse in 8 cases. The reduction in the mean score corresponds to a shrinkage in the level of sensory loss from the soles and toes to the toes.

Of 51 *plantar responses* which were definitely "extensor," 16 (31.4 per cent) became definitely flexor. The change to "flexor" occurred within three months in 8 instances and between three and six months in the remainder. Often a gradual change was observed through intermediate stages of doubtful extensor, equivocal and doubtful flexor.

Of the remaining 35 definite extensor responses, 28 were unchanged, 3 became doubtful extensor and 4 became equivocal.

Of 6 doubtful extensor responses 3 changed to flexor and 3 to extensor. 2 equivocal and 8 doubtful flexor responses became flexor. 21 definite flexor responses remained flexor.

Micturition was impaired in 26 patients of whom 13 were partly or completely incontinent of urine. Several were partly incontinent of fæces also. Difficulties ceased in 14, improved in 8, appeared temporarily in 3 and became worse in 1. Only one patient (Case 21, p. 394) still had incontinence, which recurred periodically after long intervals of normal micturition.

Comment

The average *degree* of improvement of individual symptoms and signs and the *range* of variation in improvement have just been considered.

Figs. 5, 6 and 7 show the average *rate* of improvement, which was more rapid in the upper than in the lower limbs. Astereognosis and dysfunction of the hands improved in parallel with disturbances of co-ordination and joint sense to which they were doubtless related.

Joint sense improved much more in the fingers than in the toes. Scores for gait, Romberg's sign and inco-ordination of the lower limbs ran closely parallel.

Extensor plantar responses, referable to changes in the spinal cord, were as responsive to treatment as certain symptoms and signs such as paræsthesiæ and loss of vibration sense, which some authors attribute to involvement of the peripheral nerves.

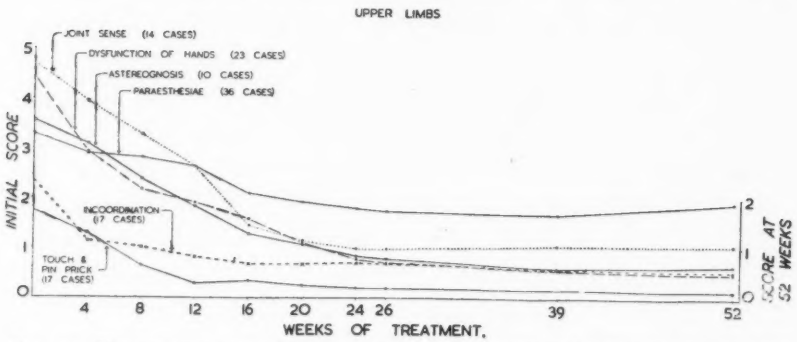

FIG. 5.—The average rate of improvement of symptoms and signs referable to the upper limbs.

The rapid improvement of disturbances of micturition is noteworthy. Inhibitory impulses from the higher centres play an important part in bladder function (Denny-Brown and Robertson, 1933). Factors responsible for improvement may include improved cerebral function due to relief of anæmia (Wilson, 1948).

When individual symptoms and signs are arranged in descending order of mean scores during the first six months, as in fig. 8, there is evidence of a tendency for the least scores to improve the most. One

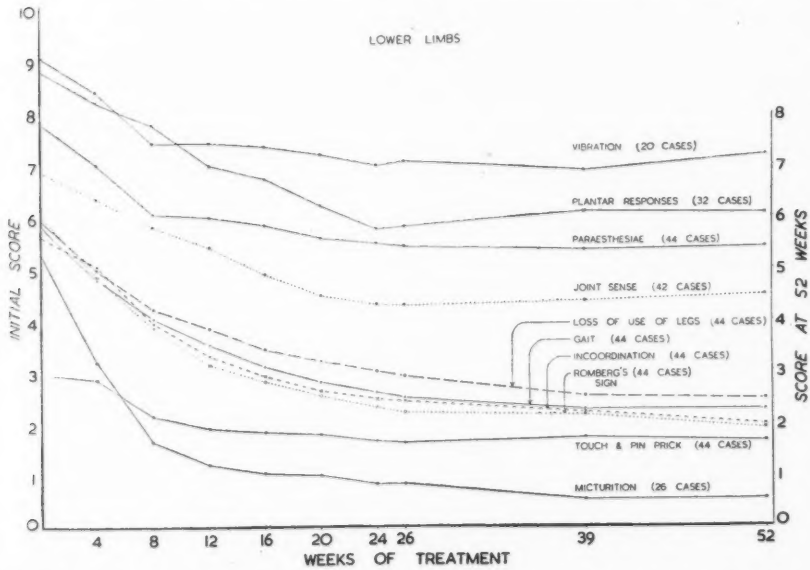

FIG. 6.—The average rate of improvement of symptoms and signs in the lower limbs, and of micturition.

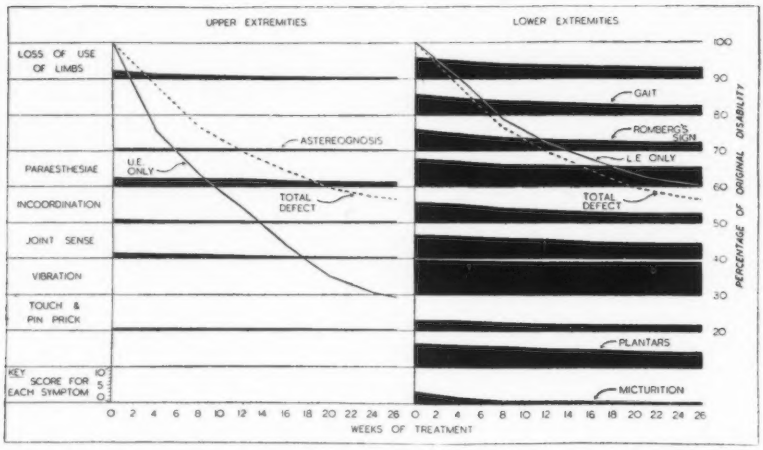

FIG. 7.—Effect of liver extract on the mean scores for individual symptoms and signs during the first six months of treatment. In this chart the means are derived from all 44 cases and not merely from the patients who had the particular symptom or sign as was the case for figs. 5 and 6. To facilitate comparison the mean total score and the mean total scores for upper and lower limbs are expressed as percentage of original disability.

exception is Romberg's sign, the score for which diminished rapidly. On the other hand, paræsthesiæ in the upper limbs and sensory loss to touch and pin-prick in the lower limbs proved refractory.

Although excluded from the total score (*see* p. 398) certain other symptoms deserve mention.

In subacute combined degeneration changes in deep reflexes, power, tone and wasting are not necessarily evidence of neurological improvement. They may be influenced, for example, by relief of anæmia or improvement in the general condition. Deep reflexes, moreover, may change from absent (through normal) to exaggerated or vice versa, according to the opposing effects of involvement of posterior and lateral columns.

Knee and ankle jerks.—Fluctuations between 3 plus and 2 plus, or 2 plus and 1 plus, were not considered significant. Variations between 2 plus and 1 plus are common in normal persons and hyperactivity up to 2 plus was regarded as within normal limits.

Return of absent deep reflexes.—This was observed in all of 20 absent knee-jerks and in 22 out of 36 absent ankle-jerks. Fourteen knee-jerks returned within three months and the other 6 between three and six months. Only 3 ankle-jerks had returned in six months, 3 more returned between six and nine months, and 10 between nine and twelve months. The remaining 6 took more than a year to return.

Usually the absent reflexes returned to normal but sometimes they became exaggerated (*see below*).

Change to hyperactive deep reflexes.—In 7 patients knee or ankle jerks, or both, changed from normal, depressed or absent to hyperactive (3 plus, with or without unsustained clonus). There was no change for the worse in the plantar responses: on the contrary, 4 extensor responses, 1 equivocal response and 1 probably flexor response became definitely flexor. Significant neurological improvement occurred in 6 out of the 7 cases and the mean reduction in total score (46 per cent) was no less favourable than in the series as a whole.

The favourable progress of other symptoms and signs suggests that the increase in deep reflexes was not due to deterioration of the cord condition. A more probable hypothesis is that improvement in lesions in the posterior columns or peripheral nerves unmasked a tendency to exaggerated deep reflexes due to pre-existing lesions in the pyramidal tracts or to a state of anxiety or emotional tension.

Relevant to this question is the fate of the deep reflexes in patients whose plantar responses changed from "extensor" to "flexor." Some had exaggerated knee-jerks and ankle-jerks which returned to normal but there were 6 absent knee-jerks and 7 absent ankle-jerks. All the knee-jerks and 5 of the ankle-jerks became normal. In these patients, at least, the increased activity of the deep reflexes could be attributed more reasonably to the amelioration of lesions in the posterior columns or peripheral nerves than to increasing pyramidal involvement.

Diminution of hyperactive deep reflexes.—In general the tendency for absent deep reflexes to become normal or exaggerated was greater than the tendency for exaggerated jerks to diminish.

A significant decrease in knee or ankle jerks occurred in only 4 patients. 2 of these deserve mention. In Case 44 active ankle-jerks became absent. This is the only example of disappearance of deep reflexes during treatment. In Case 6 hyperactive ankle-jerks with sustained clonus returned to normal. In both patients the knee-jerks changed from 2 plus to 1 plus (not significant) and the plantar responses from extensor to flexor.

Eight other patients showed some decrease in knee or ankle jerks which, although not significant in degree, was sometimes paralleled by improvement in plantar responses.

Mental symptoms.—One patient (Case 8) had delusions of persecution and was violent. The mental state became normal in five to seven weeks. In Case 20 amnesia and disorientation, which developed coincidently with an increase in other neurological manifestations and in anæmia, responded to parenteral liver therapy. In Case 30 an anxiety state with partial amnesia subsided during treatment.

Many patients had minor symptoms such as lethargy, lack of concentration or partial amnesia for recent events which usually diminished or disappeared.

Optic atrophy was present in one patient (Case 17) but in this instance liver therapy was without effect on vision.

B.—THE NEUROLOGICAL CONDITION AS A WHOLE

(1) *The total scores.*—Although a numerical method of assessment has been employed the use of the total score for comparative purposes requires some justification. Because X and Y both have a score of 100 it does not necessarily follow that their condition is equally severe in all respects, nor that they are twice as badly affected as Z who has a score of 50.

Fig. 8 shows that during the progress of the disease the scores for symptoms and signs remain very much in the same relationship to one another, with the emphasis that the more severe are the more persistent.

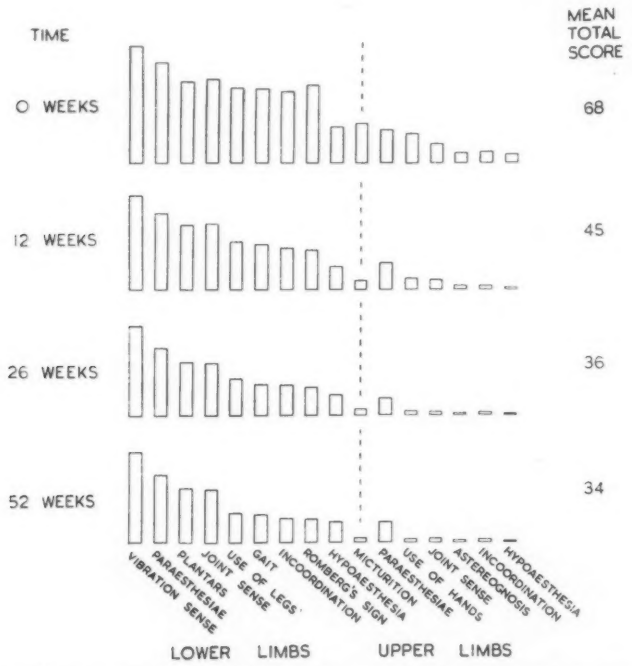

FIG. 8.—Mean scores for individual symptoms and signs arranged in descending order to show the change of pattern caused by differing rates of improvement in the first twelve months of treatment.

Dividing the cases into three groups according to severity showed that—with the minor exceptions already noted—a similar pattern is maintained in patients with varying levels of initial total score and at different stages of treatment.

(2) *Improvement curves.*—Improvement curves for cases or groups of cases were obtained by plotting successive scores as a percentage of the original disability. After an initial period of improvement the curve flattens out to a more or less horizontal line (figs. 1 and 9). In endeavouring to answer the question, "When does improvement cease?" we took as an arbitrary point the time when the level, measured as percentage of original disability, had fallen within 5 per cent of the minimum level. The mean for the "crude" group was twenty-four weeks and for the "refined" group twenty-six weeks (difference between the means not significant).

Grouping the cases according to duration of difficulty in walking gave results as follows:

Difficulty in walking	*No. of cases*	*Improvement continued for*
0 to 6 months	19	26 weeks
6 to 12 months	7	29 weeks
12 to 24 months	10	20 weeks
24 months and over ..	8	22 weeks

These findings indicate that further significant improvement is not to be expected after six months, which is therefore a suitable time for the assessment and comparison of results.

The earlier flattening out of the curves in patients who show lesser degrees of improvement is in keeping with the usual behaviour of improvement curves.

The reduction in total score in six months, expressed as percentage of original disability, ranged from 95 per cent to minus 3 per cent (mean 46 per cent). Three patients showed no significant improvement (9, 6 and minus 3 per cent).

(3) *Maintenance of the state of arrest.*—The periods during which patients had neurological examinations on a quantitative basis ranged from six months to six years, distributed as follows:

Under 1 year	*1–2 years*	*2–3 years*	*3–4 years*	*4–5 years*	*5–6 years*	*6–7 years*
7	3	10	8	11	4	1

Two patients died during the investigation, one at thirty weeks from unknown cause (Case 37) and the other, whose last examination was at 128 weeks, from "heart disease" (Case 22).

Some patients are still under observation after periods of fifteen years or more. Having attained the maximal improvement possible within the first six months, their condition remains essentially unchanged provided that adequate therapy is maintained and that there is no intercurrent illness.

The following 3 case-reports illustrate the importance of these points.

Case 30 (J. O.).—A woman now aged 70 was first treated by Professor Nattrass with whole liver in September, 1927 (*see* Ungley and Suzman, 1929*b*, Case 10). At this time she was unable to walk or even to move her legs. She improved steadily and after nineteen months could walk with the aid of a stick.

In 1933 she relapsed due to difficulty in maintaining a sufficiently high intake of whole liver. The neurological condition deteriorated until she was so helpless that she found difficulty in moving even in bed. She had incontinence of urine, extensive paræsthesiæ in upper and lower limbs, dysfunction of hands, astereognosis, defective joint sense in fingers and toes, loss of vibration sense up to the tenth dorsal spine, some sensory loss to touch and pin-prick in the hands and feet, exaggerated knee and ankle jerks and extensor plantar responses (total score 114).

Parenteral liver therapy led to gradual improvement. After thirty-nine weeks she could walk a few steps alone and 140 metres with crutches. She had very little trouble in using the hands, although paræsthesiæ persisted. Co-ordination, stereognosis, joint sense and cutaneous sensibility in the upper extremities were improved. Neurological findings in the lower limbs were almost unaltered (total score 79).

Despite a temporary setback at 100 weeks, due to infection ("influenza") her condition after five years was essentially unchanged (total score 81). To-day, twenty-one years from the institution of liver therapy, she is still able to walk with one crutch and to carry out household duties.

Two other patients are known to have relapsed while having parenteral liver therapy.

Case 21, a woman aged 35, had difficulty in walking for five months. Initially she was bedridden and incontinent. With treatment the total score fell in six months from 111 to 68 and later to levels between 35 and 45. At her best she mostly walked with a stick, but could make a fairly good attempt at walking alone on a 7·5 cm. line.

During a period of six years she had several minor relapses, either hæmatological or neurological or both. The highest neurological score was 64 at 293 weeks, with a red blood cell count of 5·14 millions per c.mm. The lowest blood count was 3·81 millions per c.mm. at twenty-one weeks and on this occasion there was no increase in the neurological manifestations. These relapses followed intercurrent infections, usually an abscess of buttock, no doubt a sequel to faulty sterilization of syringes, etc. At 317 weeks the score was 54. She could still get about with a stick, but gait and standing were not so good as they had been five years earlier. After sixteen years she can dance and skate, although she still uses a stick to walk.

Case 14, a man aged 49, had difficulty in walking for three years. The total score fell from 108 to 53 in twenty-six weeks and remained at or about this level for three years. Then he relapsed following suppuration of the foot and the total score increased slightly to 60. Red blood cells numbered 5·97 millions and hæmoglobin 93 per cent. Unfortunately the dosage of liver extract was reduced to 2 ml. per week. Six months later red blood cells numbered 5·91 millions with hæmoglobin 98 per cent but neurological symptoms had further progressed (total score 74).

Comment

During parenteral liver therapy the only neurological relapses observed coincided with infections. In the first patient maintenance dosage was adequate and infection caused only a minor set-back lasting a few weeks.

In the second patient repeated infections led to a gradual stepping-up of the level of disability. With each relapse fresh lesions appear and old ones are extended. Only part of this fresh damage is reversible.

In the third case deterioration began after infection and was not arrested by the small doses of liver extract which he was receiving.

It is possible that even in these 3 cases complete neurological arrest

might have been maintained had the dosage of liver extract been increased at the onset of infection.

(4) *The significance of the improvement.*—Several factors may have contributed to the reduction in total score:

(*a*) Apparent improvement due to training, facilitation in the performance of frequently repeated tests, compensatory mechanisms, etc. Remedial exercises were not given but some re-education was inevitable if only from the repetition of neurological tests.

(*b*) Improvement due to gain in strength and well-being and relief of anæmia (*see* pp. 398 and 406).

(*c*) Improvement due to greater use of unaffected pathways following arrest of lesions in the nervous system.

(*d*) Reversal of early lesions in the nervous system. There is presumably a stage when the lesions in the central nervous system are reversible, e.g. when myelin is degenerating but axis cylinders are intact.

(*e*) In the peripheral nerves even destruction of axis cylinders is no bar to recovery, for new axons may grow down, i.e. regeneration may occur. Several workers have found pathological changes in the peripheral nerves in pernicious anæmia but their significance in relation to the clinical picture and the results of treatment has yet to be assessed. Symptoms and signs such as paræsthesiæ and loss of vibration sense, which some authors ascribe to peripheral nerve lesions, were among the least amenable to therapy (*see* figs. 5, 6, 7 and 8).

C.—FACTORS INFLUENCING THE RESPONSE TO TREATMENT

(1) *Age and sex.*—There is no correlation with sex and only very slight correlation with age (correlation coefficient = −0·27; for 44 cases the significant level is 0·30). Thus there is a chance of slightly greater improvement in younger patients.

(2) *The duration of the disease*—as measured by the duration of difficulty in walking—is the most important factor. The greatest improvement occurred in patients with difficulty in walking for less than three months. The least improvement occurred in patients with difficulty in walking for more than two years. (Fig 9 and Table II.)

TABLE II

Duration of difficulty in walking	*Number of cases*	*Average improvement (per cent) at 26 weeks*
0 to 3 months	13	56
3 to 6 months	6	55
6 to 12 months . .	7	48
12 to 24 months . .	10	41
2 years and over . .	8	24

Fig. 10 also demonstrates graphically the influence of the duration of the disease on the response to therapy. The line expressing the cal-

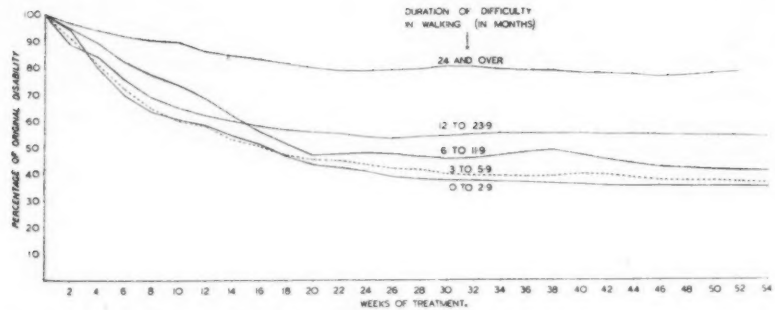

FIG. 9.—The influence of duration of difficulty in walking on the rate of recovery in subacute combined degeneration of the cord.

culated relationship shows the percentage improvement in score which may be expected in six months if the previous duration of difficulty in walking is known.

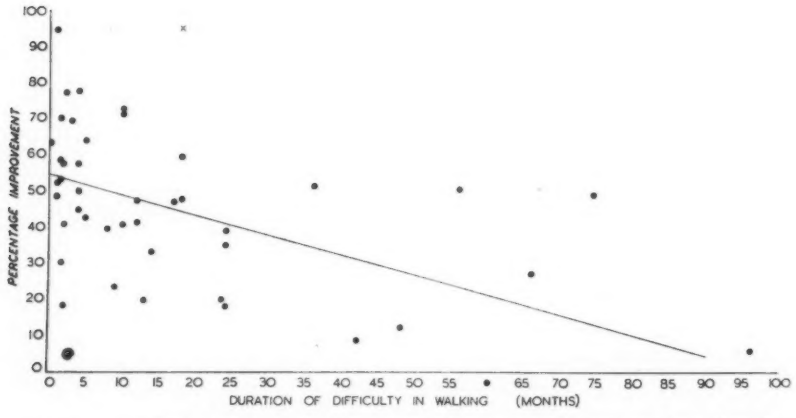

FIG. 10.—Correlation between improvement in six months and previous duration of difficulty in walking. The line expressing the calculated relationship is a guide to the degree of improvement which may be expected in cases where the duration of difficulty in walking is known. (The case marked X was omitted from the calculation.)

It is understandable that individual cases should show wide divergence between observed and expected improvement. "Duration of difficulty in walking" is not a direct expression of the duration of all lesions in the nervous system. One patient (A) with difficulty in walking for, say, four years, may have old and partly arrested lesions, while another (B) with symptoms of similar duration, may have recent active lesions in addition. The second patient (B) is likely to show the larger percentage improvement.

(3) *Severity.*—There was no correlation between severity (initial score) and percentage improvement. A patient with a high initial score was likely to show just as great a percentage improvement as a patient with a low score. On the other hand, of course, if the degree of improvement was equal in two patients, the one with the higher initial score would be left with the greater residual disability.

(4) *Previous treatment.*—Patients were divided into three groups according to treatment previously received (fig. 11).

Group A comprised 19 patients who were virtually untreated (a few had received experimental test material for ten to twenty days previously). The mean duration of difficulty in walking was six months. They were all anæmic except one, with a mean red blood cell count of 2·54 millions per c.mm.

Group B consisted of 15 patients whose previous treatment had not been sufficient to prevent the onset or deterioration of neurological symptoms. The mean duration of difficulty in walking was twice as long as in Group A. The degree of anæmia was about the same.

Group C contained 10 cases in which previous treatment had been temporarily or partially adequate. Six were unimproved or worse after receiving suboptimal amounts of liver, liver extract or hog's stomach. The other 4 had shown neurological improvement at first, but relapsed following reduction of dosage or discontinuation of treatment. The mean duration of difficulty in walking was about four years and the degree of anæmia was slight.

The improvement was satisfactory in Groups A and B, the mean total score being reduced by 49 and 55 per cent.

In Group C the mean total score was reduced by 25 per cent, i.e. improvement was much less than in the other two groups. One or more factors may have been responsible.

(i) The lesser initial degree of *anæmia* in Group C was probably not an important factor.

(ii) *Severity* was not a factor—the initial score was no higher in Group C than in the other groups.

(iii) The *duration* of difficulty in walking was much longer in Group C than in the other groups. This alone might account for the lesser degree of improvement.

(iv) It is unlikely that *previous treatment* is deleterious in itself, since patients in Group B whose spinal cord lesions were not arrested did quite as well as those in Group A who were untreated.

In Group C, however, the previous treatment was temporarily or partially adequate, and of long duration. We have shown elsewhere that adequate treatment leads to improvement which is practically complete in six months, leaving a residuum of symptoms and signs, presumably attributable to irreversible lesions in the nervous system. In Group C, therefore, a higher proportion of the lesions in the nervous system were probably already arrested and irreversible, thus limiting

the possibilities of further improvement. In patients who had improved to the maximal extent and then relapsed through neglecting treatment only the recent acute lesions would be susceptible to improvement.

To summarize, the patients who improved the least were treated cases with difficulty in walking for more than two years. The initial red blood cell count was usually high. The significant factor, however, was probably the state of partial arrest of the lesions in the nervous system to which duration and previous treatment would contribute.

(5) *Arteriosclerosis and hypertension.*—These conditions were common but did not appear to affect the degree of neurological improvement during liver therapy.

(6) *Infection.*—In 2 patients pernicious anæmia with subacute combined degeneration developed during the course of a long continued septic infection, namely empyema (Case 42) and suppuration of an upper limb following injury (Case 27).

In this series low-grade urinary infections and dental sepsis did not prevent neurological improvement. Possibly the doses of liver extract were large enough to meet any added requirements for anti-pernicious anæmia factor caused by these complications.

On the other hand, infections did seem to play a part in the relapses which occurred in Cases 14 and 21 (*see* p. 394). These patients were receiving maintenance doses of liver extract which were smaller than those given in the first six months of treatment. The need for increased dosage during infections is emphasized.

(7) *Degree of anæmia.*—There are several aspects to this problem.

(i) *How much of the neurological picture in pernicious anæmia is due to anæmia? Does relief of anæmia account for the neurological improvement?*

Patients who are anæmic from any cause may have transient paræsthesiæ, weakness and loss of muscular tone and bulk, disorientation and amnesia or impairment of vision. With the exception of paræsthesiæ, none of these symptoms are included in the total score for neurological defect.

It has been argued that a weak person is ataxic and inco-ordinate and may be unable to walk. On the other hand we have examined many patients with uncomplicated pernicious anæmia having red blood cell counts within the range of those observed in this series who have shown normal, or at the most, very slightly impaired co-ordination in the tests described in the Appendix.

Nevertheless, relief of anæmia might conceivably influence the results, either directly or indirectly: directly, if improved blood supply led to better conduction in partially damaged nervous pathways in the central or peripheral nervous system; or indirectly if increasing strength and mental alertness led to better performance in neurological tests.

One approach to this problem has been to observe the effect of blood transfusion on the neurological condition (p. 406). In 5 cases there were

control periods during which anæmia was relieved by blood transfusion. Although 3 patients showed decrease in paræsthesiæ, the neurological condition as a whole improved slightly in only 1 case. Three were unchanged or slightly worse and 1 became considerably worse.

In another category is the coincidence of hæmatological improvement with neurological relapse in some patients treated with pteroylglutamic acid (p. 404).

Dissociation between hæmatological and neurological improvement is occasionally observed in patients receiving inadequate liver therapy. For example, subacute combined degeneration progressed in a patient (Case 34) who had taken inadequate amounts of liver which were, however, enough to bring the red blood cell count to 5·02 millions per c.mm. With adequate therapy the total score for neurological defect was reduced by 35 per cent in six months.

It is, of course, well known that the progress of neurological manifestations does not necessarily run parallel with the anæmia. Pernicious anæmia may exist without neurological manifestations, and subacute combined degeneration without anæmia.

In Case 16 the initial red blood cell count was 4·57 millions per c.mm., yet the patient showed distinct neurological improvement, the total score being reduced by 41 per cent in six months.

Relevant to this subject is the influence of the initial level of red blood cells on the degree of neurological improvement (below).

(ii) *Is the initial red blood cell count a factor influencing the degree of neurological improvement which occurs during liver therapy?*

In fig. 11 percentage improvement is plotted against initial red blood cell count, the cases being divided into Groups A, B and C according to previous treatment.

Taking the series as a whole there is significant correlation between high red blood cell counts and small improvement (correlation coefficient = −0·46). A substantial part of this correlation derives from the small improvement of patients in Group C. Their high red blood cell counts were due to previous treatment. The small improvement might be accounted for by their long duration and/or partial arrest of nervous lesions by previous treatment.

Taking the groups individually, the correlation is not apparent within Group C itself.

In Group B there is a significant correlation (correlation coefficient = −0·52). Some of these patients had had enough treatment to raise the red blood cell level and the possibility of partial arrest of nerve lesions cannot be excluded.

In Group A the patients were virtually untreated. Although there is a possible correlation (correlation coefficient = −0·14) it is very slight compared with that observed for a factor such as duration.

We may conclude from these findings that the initial red blood cell count is not in itself a significant factor influencing the degree of neurological improvement to be expected from liver therapy.

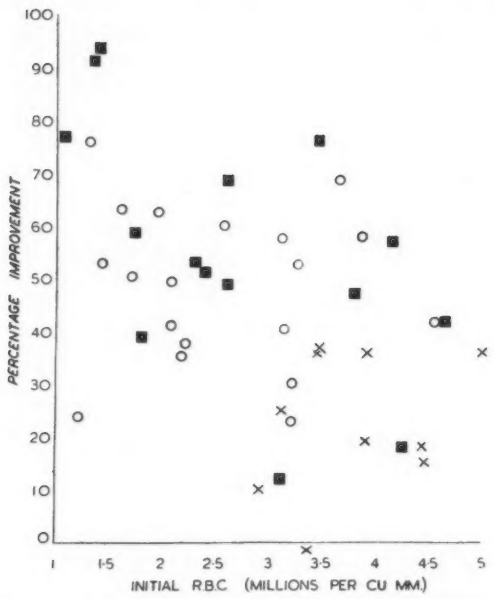

FIG. 11.—The relation between percentage improvement and initial red blood cell count. Solid squares (Group A): untreated cases. Circles (Group B): patients who had had very little previous treatment. Crosses (Group C): patients who had previously had temporarily or partially adequate treatment.

(iii) *Is the amount of neurological improvement related to the level of red blood cells attained?*

To this question the answer is that there was no correlation between percentage improvement in the total score for neurological defect and the level of red blood cell count attained in six months (correlation coefficient = 0·002). Patients whose red blood cell counts failed to reach a level of 5 millions per c.mm. did no worse than those whose counts exceeded this level.

(iv) *Is it necessary to maintain the red blood cell count at 5 millions to ensure arrest of subacute combined degeneration?*

For each patient the mean of all red blood cell counts between six and twelve months was obtained (Table III).

The findings show that red blood cell counts below 5 millions per c.mm. were common in patients in whom sufficient liver extract was given to maintain arrest of subacute combined degeneration. Indeed there were 14 out of 44 patients in whom the means of all the red blood cell counts between six and twelve months were below 5 millions (Table III, line 1).

As many as 10 out of 44 patients never attained a red blood cell

TABLE III

	R.B.C. mean of 44 cases	*Number of patients with R.B.C. in this range* 3·5–3·99	4·0–4·49	4·5–4·99	5·0–5·49	5·5–5·99	6·0–6·49	6·5–6·99
Mean of all counts between six and twelve months	5·13	0	4	10	14	14	2	0
Lowest single count from six months onwards ..	4·86	1*	9	15	15	3	1	0
Highest single count from six months onwards ..	5·58	0	1	9	9	14	8	3

*Relapse of anæmia was due to intercurrent infection at forty-one weeks in Case 21. There was no increase in the neurological manifestations in this instance.

count of 5 millions per c.mm. at any time during the period of observation from six to twelve months (Table III, line 3).

It is obvious from these figures that even with intensive liver therapy red blood cell counts of over 5 millions per c.mm. are not maintained or even attained in all cases; nor is this essential for the arrest of subacute combined degeneration.

The range of red blood cell counts in patients receiving large maintenance doses of liver extract for subacute combined degeneration appears to be similar to that which might be found in a random sample of healthy men and women of the same age-groups. The lower figures found in some instances are not necessarily evidence of inadequate dosage or poor response to liver extract.

DOSAGE

The above findings show the fallacy of the commonly reiterated statement: "To ensure prevention or arrest of neurological manifestations in pernicious anæmia it is essential to maintain a red blood cell count of 5 millions." The fallacy probably arose from taking a mean and using it as a normal (Ryle, 1947).

It is probably unwise then to link dosage too closely with the red blood cell level. Certainly a subnormal red blood cell count with a raised mean corpuscular volume calls for increased dosage—so does a recurrence of sore tongue. But in subacute combined degeneration it is desirable to go beyond these requirements and to base dosage on the amounts needed to arrest the nervous lesions.

Liver preparations vary so much in potency that volume alone is an inadequate guide to dosage. With microbiological assays to supplement clinical tests, however, it should soon become standard practice to prescribe liver extracts in terms of their vitamin B_{12} content.

The hæmatopoietic potency of the extracts used in this investigation was measured (Ungley, Davidson and Wayne, 1936; Ungley, 1936, and unpublished observations). A useful index is the single dose required to produce a rise in blood cells in fifteen days which is satisfactory when compared with the expected response according to the

"average" formula of Della Vida and Dyke (1942). Subsequent work has shown that responses of this order can be obtained by the administration of 10 micrograms of vitamin B_{12} (Ungley, 1949c). The margin of error is wide because of the variation in hæmatopoietic response between different individuals, but broadly speaking the average dose of liver extract administered to patients with subacute combined degeneration in this series was hæmatopoietically equivalent to about 4 times the above-mentioned single dose. These clinical findings together with the results of microbiological assay on certain of the liver extracts used suggest that the average weekly dose may have contained about 40 micrograms of vitamin B_{12}. This was the level of dosage subsequently adopted for the pure material itself (Part II).

Summary and Conclusions

(1) In 44 patients with subacute combined degeneration receiving parenteral liver therapy, 471 examinations for the quantitative assessment of neurological status were made in periods of observation ranging from six months to six years. Two patients died from intercurrent illness.

(2) There was no statistical difference between the effects of crude and refined liver extracts.

(3) In general, the symptoms and signs with the least scores improved the most. The upper limbs improved more than the lower. Use of the hands and recognition of objects improved coincidently with disturbances of co-ordination and joint sense. Joint sense returned more often in the fingers than in the toes. Improvement curves for gait, Romberg's sign and co-ordination of the lower limbs ran closely parallel. Disturbances of micturition diminished rapidly.

(4) Extensor plantar responses, referable to lesions in the spinal cord, improved at least as much as paræsthesiæ and loss of vibration sense which are attributed by some authors to lesions in the peripheral nerves.

(5) Manifestations not included in the total score for neurological defect include mental symptoms, muscular power, tone, wasting, tenderness and deep reflexes. The tendency for absent deep reflexes to become normal or exaggerated was greater than the tendency for exaggerated jerks to diminish. Absent knee-jerks reappeared within six months; ankle-jerks sometimes took longer to return or did not reappear at all.

(6) Improvement curves based on total scores, i.e. on the sum of the scores for individual symptoms and signs, flattened out in about six months, during which time 95 per cent of the improvement took place.

(7) Percentage reduction in total score in six months ranged from 95 per cent to minus 3 per cent (mean 46 per cent). Improvement was significant in 41 cases. The remaining 3 patients, who had been treated previously, showed no significant change.

(8) After six months the state of arrest was maintained except in 3 patients in whom relapse followed intercurrent infection. Even these relapses could probably have been prevented by increasing the dosage of liver extract at the onset of the infection.

(9) Factors contributing to the improvement probably include training, gain in strength, recovery of lesions in the peripheral nerves, reversal of early lesions in the central nervous system and arrest of others, followed by greater use of unaffected pathways.

(10) The influence of the duration of the disease on the response to therapy has been demonstrated graphically. A line expressing the calculated relationship shows the percentage improvement in score which may be expected in six months if the previous duration of difficulty in walking is known.

(11) Previous therapy was also important. Treatment had been nil or negligible in 19, totally inadequate to prevent or arrest neurological manifestations in 15 and temporarily or partially adequate in 10. The patients who improved the least were the third group, i.e. treated cases, all of long duration. Initial red blood cell counts were usually high. The significant factor, however, was probably the state of partial arrest or irreversibility of the lesions in the nervous system, to which duration and previous treatment would contribute.

(12) Factors of little or no importance were age, sex, severity, arteriosclerosis and hypertension and degree of anæmia.

(13) It is not enough to base requirements for potent material on the amounts needed to maintain normal red blood cell levels or to prevent sore tongue. Dosage must be based on the amounts needed to improve or arrest the nervous lesions.

(14) The weekly dose of liver extract adequate for most patients in this series is estimated to have been hæmatopoietically equivalent to about 40 micrograms of vitamin B_{12}. After six months half this quantity is usually sufficient but amounts should be increased if there is any indication of relapse, whether neurological or otherwise, or if intercurrent infection supervenes.

PART II: TRIALS WITH VITAMIN B_{12}

Amelioration of paræsthesiæ and inco-ordination in patients with pernicious anæmia undergoing liver therapy was at first attributed to improvement in general condition and relief of anæmia (Minot and Murphy, 1926).

An investigation of 61 cases of subacute combined degeneration led Ungley and Suzman (1929) to believe that liver had a direct effect on the neurological manifestations. It appeared that more potent material was required to arrest the nervous lesions than to establish and maintain normal red blood cell levels. Later, brain and desiccated stomach also proved to be efficacious.

Early efforts to isolate the anti-pernicious anæmia factor provided

fractions which were effective in subacute combined degeneration if given orally in adequate amounts, but striking results were not demonstrated until the difficulties of maintaining adequate dosage were overcome by parenteral administration (Ungley, 1934).

A search amongst the other constituents of liver for the hypothetical neuropoietic factor excluded vitamin A, iron and vitamin B_1 (Suzman, Muller and Ungley, 1932; Ungley, 1938 and 1939). Two patients received vitamin B_1 in the absurdly high dosage of 50 mg. daily by injection for six weeks without neurological improvement (unpublished observations).

In 1946 the availability of a synthetic agent effective for blood regeneration in pernicious anæmia—pteroylglutamic (folic) acid—seemed to offer prospects of deciding the identity or non-identity of the hæmatopoietic and "neuropoietic" principles.

In two patients with subacute combined degeneration (Cases 45 and 46) pteroylglutamic acid relieved the anæmia but appeared to have no effect on the neurological condition. After six weeks the experiments were discontinued: reports by other workers were mostly unfavourable and in some instances the development of nervous lesions was precipitated (Ross, Belding and Paegel, 1948; Davidson and Girdwood, 1948; Wilkinson and Israels, 1948; and others).

These findings showed that a presumably pure substance could promote hæmatopoiesis in pernicious anæmia without arresting the lesions in the nervous system. Nevertheless, the role of folic acid in Addisonian pernicious anæmia was, and still is, obscure. Folic acid was evidently not the effective agent in liver extracts, which usually contained quite negligible amounts. The question whether hæmatological and neurological disorders in the naturally occurring disease arose from deficiency of the same or of different substances remained unanswered.

Meanwhile I had been collaborating with Dr. E. Lester Smith who was making rapid progress in the isolation of anti-pernicious anæmia factors from liver. By 1947 it became evident that hæmatopoietic activity in liver fractions was closely associated with red colour, and tests to determine the efficacy of these red pigmented extracts in subacute combined degeneration were commenced.

In April 1948 independent work in America by Rickes, Brink, Koniuszy, Wood and Folkers, who were greatly helped by microbiological assays (Shorb, 1947), led to the isolation from liver of a red crystalline anti-pernicious anæmia factor, which they termed vitamin B_{12}.

In the same month Lester Smith announced the preparation of red pigmented material which my clinical tests had shown to be effective both in pernicious anæmia and in subacute combined degeneration (Lester Smith, 1948; Ungley, 1948*a*). Partition chromatography showed the presence of two red components, a fast-moving and a slow-moving band.

In May 1948 the fast-moving red component was isolated in the form of red crystals, which appeared to be identical with vitamin B_{12} (Lester Smith and Parker, 1948).

By July there was evidence that the single dose of this pure red crystalline factor required to produce a satisfactory rise of red blood cells lasting fifteen days was in the region of 10 micrograms. Like the less pure red pigmented material used previously it appeared to be as effective as liver extract in the treatment of subacute combined degeneration (Ungley, 1948*b*).

The present paper confirms these preliminary observations and describes results obtained in 8 cases.

Material and Methods

The patients included 4 men and 4 women with ages ranging from 48 to 65 (mean 57) years. All had classical pernicious anæmia with sufficient involvement of the nervous system to interfere with gait and co-ordination. 2 were slightly, 4 moderately and 2 severely affected. One patient had had liver therapy on and off for eleven years (very little for one year); 7 were hitherto untreated. 3 patients had difficulty in walking for two years or more (two, two and eleven years); in the others the duration was two, two, three, eight and twenty months. The degree of anæmia is shown in Table IV, p. 406.

Selection of cases and dietary restrictions are described in Part I. 5 patients had control periods during which transfusions were given (*see later*).

The quantitative method of neurological assessment was used, the total number of complete examinations in 8 patients being 158 (24 before and 134 during treatment).

Treatment

Dosage of the earlier preparations which were amorphous and contained two red pigments is expressed as equivalent (on a colorimetric basis) to so many micrograms of red crystalline material. After the isolation of the fast-moving red component in May 1948 the pure crystalline substance itself was used. Administration was intramuscular; there were no untoward reactions.

The first 4 patients have been treated for fourteen to nineteen months, at first with the less pure material, but latterly (for thirteen months) with the crystalline substance, vitamin B_{12}.

The remaining 4 patients, observed for nine to thirteen months, have received pure vitamin B_{12} from the outset. The usual weekly dose was 40 micrograms, but in 2 patients (Cases 52 and 53) the amount was temporarily increased to 80 micrograms.

Note.—By a combination of partition chromatography on paper with microbiological assay on solid medium Cuthbertson and Lester Smith (1949) showed that liver extracts contain four substances related to vitamin B_{12}.

(*a*) A fast-moving red component.
(*b*) A slow-moving red component.
(*c*) An unidentified substance ("band 3").
(*d*) Thymidine.

The fast-moving component is the one already isolated in crystalline form (Lester Smith and Parker, 1948) and found to be identical with vitamin B_{12}. Recently the slow-moving component has also proved to be effective in a dose colorimetrically

equivalent to 10 micrograms of the crystalline factor (Ungley, 1949*c*). Thymidine, on the other hand, appears to be without effect in pernicious anæmia (Ungley, 1949*b*).

The red pigmented material used prior to June 1948 was free from "band 3" and thymidine but contained both the two active red pigments.

The change from less pure to pure red pigmented material was not accompanied by any alteration in the rate of improvement in our patients with subacute combined degeneration (*see* Cases 47 to 50). Patients treated with red crystalline material from the beginning (Cases 51 to 54) have done at least as well as those who first had impure material.

Results

Hæmatopoietic and General Effects

(*a*) *Control periods.*—5 patients had control periods of one and a half, two, five, six and eight weeks during which anæmia was relieved by transfusions of red blood cell concentrates. The transfusions relieved symptoms referable to anæmia, when present, but did not noticeably affect appetite, well being or sore tongue. The extent to which the red blood cell counts were raised is shown in Table IV and in figs. 13, 15, 17, 18 and 19.

TABLE IV.

Red blood cell counts in millions per c.mm.

Case No.	*Before transfusion*	*After transfusion (highest)*	*Before A.P.A.F.*	*Days to reach normal R.B.C. levels (4½–5 millions)*
47	1·49	3·90	2·73	21
48			1·79	66
49			1·98	36
50	3·25	5·19	4·39	7
51			2·33	48
52	3·27	5·35	4·59	0
53	1·80	3·97	3·6	26
54	3·21	4·93	4·84	0
Mean	2·60	4·67	3·28	

(*b*) *Effect of red anti-pernicious anæmia factors.*—Hæmatopoietic effects of vitamin B_{12} are described more fully elsewhere (Ungley, 1949*c*). In patients whose initial red blood cell counts were low enough, injections of red pigmented or crystalline material were followed by the classical hæmatopoietic response. Megaloblasts in the marrow matured rapidly (Lorriman, 1948) and reticulocyte responses were up to expected levels. The rate of increase of red blood cells was satisfactory except in one patient (Case 48) who was slow to reach normal figures.

There were the usual accompaniments of remission—well being, gain in appetite and weight, relief of sore mouth and of gastro-intestinal symptoms, if present, and repapillation of the tongue.

Neurological Effects

(*a*) *Control periods and effects of transfusion.*—Of the 5 patients who were transfused 3 noted a diminution of paræsthesiæ which in one instance (Case 47) led to a small decrease in total score. Apart from this

none of the patients showed improvement and one (Case 52) became considerably worse.

(*b*) *Effect of red anti-pernicious anæmia factor.—Difficulty in walking:* Walking improved in 4 patients whose disability was moderate or severe (scores 4 → 1, 7 → 4, 8 → 4, 6 → 3) and became normal in the others, whose disability was slight (3, 3, 2, 1).

Gait: One patient had a very slight defect in gait which disappeared. 5 patients had a moderate defect, being unable to walk on a 7·5 cm. base; the defect became slight in 1, very slight in 3 and disappeared entirely in 1. 2 patients had a severe defect and need strong support to walk even a short distance; now both can walk unaided but make 10 to 19 mistakes in pacing 23 metres on a 7·5 cm. line.

Romberg's sign: 1 patient had no defect and another had a slight defect which disappeared.

4 patients had a strongly positive Romberg's sign which became slight in 3 and negative in 1.

2 patients had severe disability—1 could not stand at all and 1 was unsteady even with feet apart and eyes open. Both can now stand alone in Romberg's test with some sway but no overbalancing.

Difficulty in using the hands disappeared in 2 patients and was unchanged in a third.

Slight *difficulty in recognizing the presence or nature of objects* placed in the hand disappeared in four instances; marked difficulty improved in one.

Slight or occasional difficulties in *micturition*, present in 3 patients, disappeared.

Paræsthesiæ: 6 patients had paræsthesiæ of varying extent and severity in the upper limbs. These disappeared completely in 2 cases, almost completely in 2, diminished in 1 and were unchanged in 1. The decrease in the mean score from 3·5 to 0·5 is equivalent to recession of constant paræsthesiæ in the whole of the fingers to transient paræsthesiæ in the finger ends.

7 of the 8 cases had paræsthesiæ in the lower limbs, sometimes extending on to the trunk. Paræsthesiæ disappeared completely in 2 and almost completely in 3 patients, and have diminished in the other 2. The decrease in mean score from 5·9 to 1·5 is equivalent to a shrinkage in extent of paræsthesiæ from the level of the mid-calf to the toes and distal part of the sole.

3 patients had *inco-ordination* of the upper limbs which became normal.

In 1 patient very slight inco-ordination of the lower limbs disappeared. 3 patients had slight to moderate defects in co-ordination which became very slight. Severe inco-ordination, present in 4 patients, became slight in each case.

3 patients had definitely impaired *joint sense* in the fingers which became normal in 2 and improved in 1. All 8 patients had defects in

joint sense in the toes which ranged from moderate to severe. Improvement was definite in 2 and doubtful in 1 instance; in 5 patients there has been no change. The fall in the mean score from 8·6 to 7·4 is hardly significant, being equivalent to a similar decrease in the number of mistakes made in 20 tests.

All patients had loss of *vibration sense* in the lower extremities at least as high as the lumbar vertebræ. Sensibility returned almost completely in 2, partially in 4, and slightly or not at all in 2 cases. The decrease in the mean score from 10 to 6·4 corresponds to a return of vibration sense in lumbar spine, sacrum and anterior superior iliac spines.

Sensory loss to light *touch* in the hands, noted in 1 patient, did not improve. Loss in the lower limbs, definite in 3 patients, improved slightly in 2 and was unchanged in the third.

Hypoalgesia to *pin-prick* in the hands improved in the only patient who showed this sign. In the lower limbs 4 patients had definite loss to pin-prick which improved in each instance.

5 patients had definite defects in recognition of *figure writing* in the palms, the mean score being equivalent to 5 mistakes out of 10 tests on each side (*see* p. 425). Recognition became normal in 4 cases and in the fifth the score was reduced from 8 to 3. All the 8 patients had defects in recognition of figure writing in the soles. Recognition became normal in 3 instances, much improved in 2, and almost unchanged in 3. The reduction in the mean score from 8 to 4 is equivalent to a corresponding reduction in the number of mistakes in 10 tests on each side.

5 patients had *extensor plantar responses* on one or both sides. 1 patient (Case 53) had an equivocal, later consistently extensor response, which is now flexor. In another (Case 54) bilateral extensor responses were obtained; after the eleventh week the usual response was a clear-cut flexor from both borders of the left foot, the right plantar response remaining extensor. In the other 3 cases the extensor responses are unaltered.

This concludes the findings quantitatively assessed and included in the total score. Certain other findings are of interest.

Only 1 patient (Case 52) had *tenderness* over the peroneal nerve trunks. In this patient the calf muscles were tender throughout the control period of six weeks and for the first nine weeks of treatment. In another patient (Case 53) slight to moderate tenderness of calf muscles has persisted up to twenty-seven weeks. In 3 patients (Cases 48, 50, 54) tenderness was elicited only on isolated occasions. In the remaining 3 patients the calves were not tender.

Muscle tone was increased in the lower extremities in 3 patients (Cases 48, 53 and 54). Consistent differences as the result of treatment were not observed.

In 1 patient (Case 50) sluggish *knee-jerks* returned to normal.

Another (Case 54) had exaggerated knee-jerks which remained hyperactive. The remaining patients had normal knee-jerks.

2 patients (Cases 53 and 54) had hyperactive *ankle-jerks* which became normal. In Case 52 normal ankle-jerks disappeared during a control period of six weeks; at twenty-six weeks the ankle-jerks were again normal. 4 patients (Cases 47, 48, 50 and 51) had absent ankle-jerks throughout.

Total Score for Neurological Defect

Changes in the total scores (figs. 13 to 19) were compared with the "expected" improvement based on 44 cases treated with liver extract, taking into account the duration of difficulty in walking which is the main factor influencing the response to treatment (fig. 10). Of the 8 cases, 4 have exceeded the expected rate of improvement, 2 have attained it and 2 are just short of it. The average improvement was 56 per cent compared with the expected 43 per cent.[1]

In fig. 12 the effects of liver extract and red anti-pernicious anæmia factors are compared graphically.

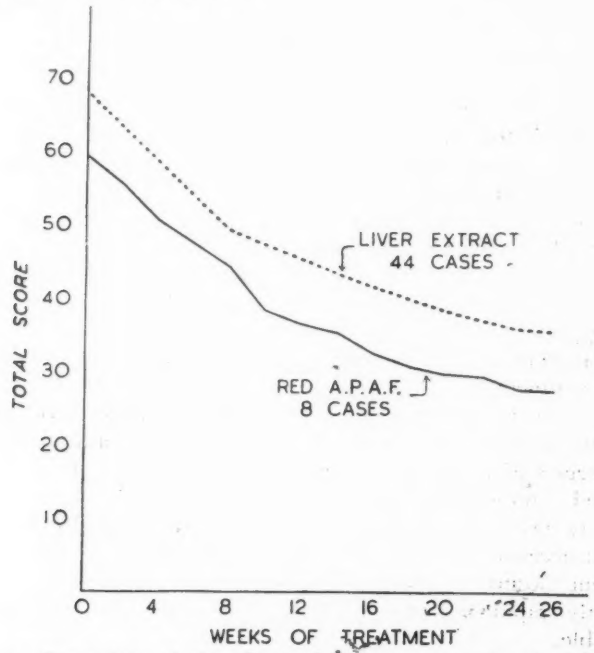

Fig. 12.—Comparison of the effects of liver extract and red anti-pernicious anæmia factors (vitamin B_{12} or vitamin B_{12} concentrates) based on the changes in the mean total scores for neurological defect.

[1]To allow comparison with the results obtained with liver extract (Part I) figure writing has been omitted from the total scores (except in figs. 13 to 19).

Discussion

Experience with folic acid has stressed the need for caution in judging the efficacy of an agent against neurological manifestations of pernicious anæmia. While prolonged observation of a large number of patients is necessary to determine whether such an agent will prevent the development of lesions in the nervous system, its effects can be observed directly in a much shorter period by treating established cases of subacute combined degeneration (Ungley, 1948*a*).

This is the method adopted here. The requisite data were obtained by the frequent examination of a small number of patients under controlled conditions using well tried quantitative methods (*see* Appendix p. 422).

Control periods during which transfusions were given limited the possible error from spontaneous remission or from neurological improvement due to mere relief of anæmia.

In general, the improvement in the mean scores for various symptoms and signs was greater than in the previous series. Particularly noticeable was the greater improvement of paræsthesiæ and of vibration sense; on the other hand, joint sense in the toes improved less. Since the number of cases was small these may well have been chance differences.

It is clear that Lester Smith's red crystalline anti-pernicious anæmia factor is as effective as liver extract in subacute combined degeneration. According to reports from America, the vitamin B_{12} of Rickes, Brink, Koniuszy, Wood and Folkers (1948)—now known to be identical with Lester Smith's—is also effective (Berk, Denny-Brown, Finland and Castle, 1948; Hall and Campbell, 1948; Bethell, Meyers and Neligh, 1948). In the case described by Berk and his co-workers, neurological manifestations of brief duration disappeared almost entirely in a short time, suggesting that in the spinal cord a rapidly reversible "biochemical lesion" precedes structural degeneration from which recovery is slower and less complete.

Since a chemically pure crystalline substance is effective not only in pernicious anæmia but in subacute combined degeneration of the cord, the existence of a separate "neuropoietic" factor need no longer be postulated. A possible criticism is that the anti-pernicious anæmia factor may have acted by increasing appetite and thereby the intake of nutrients necessary for the integrity of the nervous system. The improvement occurred despite dietary restrictions, however, and was sufficiently rapid in some cases to render such an indirect action improbable.

Since the results were at least equal to those in the previous series, it is improbable that impurities accompanying the red pigments in the liver extracts used had any significant adjuvant effect.

Lester Smith's second red pigment, the slow-moving component, is active for hæmatopoiesis in pernicious anæmia but has yet to be tested

in subacute combined degeneration. Liver extracts contain both red pigments and if properly standardized are quite as satisfactory as pure material for routine therapy. A possible exception is in patients hypersensitive to liver extracts (Berk *et al.*, 1948).

The results obtained with weekly doses of 40 micrograms of the red crystalline material are in agreement with those obtained with amounts of liver extract equivalent in hæmatopoietic potency (Part I).

Summary and Conclusions

(1) An account is given of attempts to determine the nature of the agent in liver effective in subacute combined degeneration, culminating in successful trials with a red crystalline anti-pernicious anæmia factor, vitamin B_{12}, one of the red pigments contained in Lester Smith's less pure earlier material.

(2) 8 patients with subacute combined degeneration were studied by the quantitative method described in the Appendix. 2 were slightly, 4 moderately and 2 severely affected. The duration of difficulty in walking ranged from two months to eleven years.

(3) The first 4 patients, who were given the less pure material initially, have been treated for fourteen to nineteen months, for the past thirteen of which they have received the pure substance. The remaining 4 patients, treated for nine to thirteen months, received red crystalline material from the outset.

(4) Of the 5 patients who were transfused, 3 noted a diminution of paræsthesiæ, which in one instance led to a small decrease in total score. Apart from this, none of the patients showed improvement and one became considerably worse.

(5) The improvement observed after vitamin B_{12} was compared with the "expected" improvement based on 44 cases treated with liver extract (*see* Part I). This took account of the duration of difficulty in walking, which is the main factor influencing the response to treatment.

(6) 4 of the 8 cases exceeded the expected rate of improvement, 2 attained it and 2 fell just short of it. The average reduction in total score for neurological defect was 56 per cent compared with the "expected" 43 per cent.

(7) Vitamin B_{12} is therefore as effective as liver extract not only in pernicious anæmia but in subacute combined degeneration.

(8) The existence of a separate "neuropoietic" factor need no longer be postulated.

(9) Except perhaps for patients who have become sensitized to some impurity in liver fractions, the pure substance has no advantage over commercial liver extracts, particularly if their potency is determined clinically and microbiologically and expressed in terms of micrograms of vitamin B_{12}.

(10) Weekly doses of 40 micrograms or their equivalent in liver extract are usually adequate in the first six months, with half these

amounts for maintenance thereafter. At the least sign of relapse, however, or if intercurrent infection supervenes, dosage should be increased until complete arrest of the neurological condition is assured.

Case Reports

Case 45 (B. W.), an ex-miner, aged 69, had noticed sore tongue, paræsthesiæ and difficulty in walking for eight months. He had not had liver therapy.

He was given 20 mg. pteroylglutamic acid daily by mouth. Reticulocytes reached a peak of 5·6 per cent. Red blood cells increased from 2·84 to 3·48 millions per c.mm. in fifteen days and after six weeks numbered 4·48 millions per c.mm. Appetite improved but the tongue was still sore.

Difficulty in walking, gait and Romberg's sign did not improve. Paræsthesiæ diminished slightly in the hands and remained unchanged in the lower limbs. Inco-ordination in the upper and lower limbs improved very slightly. Joint sense in the toes did not improve. Vibration sense remained absent in the lower limbs, pelvis and lumbar vertebræ. Patchy loss of sensation to touch in the feet did not alter significantly.

He now received weekly injections of 5 ml. of anahæmin. The tongue became repapillated and was no longer sore. In six weeks the neurological condition did not alter. Scores for total neurological defect did not vary significantly from a level of 45 to 50 throughout both periods.

Case 46 (E. M.) a housewife, aged 47, gave a history of paræsthesiæ with difficulty in walking and in using the hands for eighteen months. She had not had liver therapy. A low-grade urinary infection was present (*Bacillus coli*).

She was given pteroylglutamic acid 20 mg. daily by mouth. Reticulocytes reached a peak of 4·4 per cent. Red blood cells increased from 2·94 to 3·74 millions in fifteen days and after six weeks numbered 4·48 millions.

Paræsthesiæ, which extended to the elbows and to the abdomen, did not alter appreciably. Incontinence of urine ceased and after the first week dysuria was slight. Dysfunction of the hands did not improve. Severe inco-ordination of the lower limbs improved very little. Joint sense remained absent in the toes. Vibration sense remained absent up to and including the lumbar vertebræ. Hypoæsthesia to touch in the toes and distal parts of the soles persisted. Doubtful extensor plantar responses became definitely extensor. She remained unable to walk or stand without strong support.

Treatment was now changed to 5 ml. of anahæmin twice weekly. In the next six weeks inco-ordination and joint sense improved; other symptoms showed little change.

Case 47 (P. P.), male clerk, aged 48. Pernicious anæmia and unsteady gait since 1936. Liver therapy irregular—negligible for eighteen months. Relapsed four months ago.

Following blood transfusions there was little change in neurological condition apart from relief of slight and transient paræsthesiæ in the lower limbs.

The effect of red pigmented material (vitamin B_{12} concentrate) is shown (fig. 13). Initially he was unsteady at times. After 24 weeks he walked normally even in the dark. The gait, which was ataxic on a broad base, became almost normal after eight weeks. In Romberg's test he overbalanced almost at once. After eight weeks he no longer overbalanced but there was some sway. Occasional slight tingling in the finger ends ceased after fifteen weeks; transient tingling in the legs, noted initially, did not recur. Moderately severe inco-ordination became slight after ten weeks. Joint sense remained absent in the great toes. There was no return of vibration sense. Sensation to touch remained defective, particularly over the thick skin of the feet and legs. Patchy blunting to pin-prick gradually improved. Recognition of figure writing became normal in the palms but remained defective

in the soles. Knee-jerks were normal. Ankle-jerks remained absent. The right plantar response remained extensor.

For the past year, i.e. from the 28th week onwards, he has received crystalline vitamin B_{12} without neurological relapse.

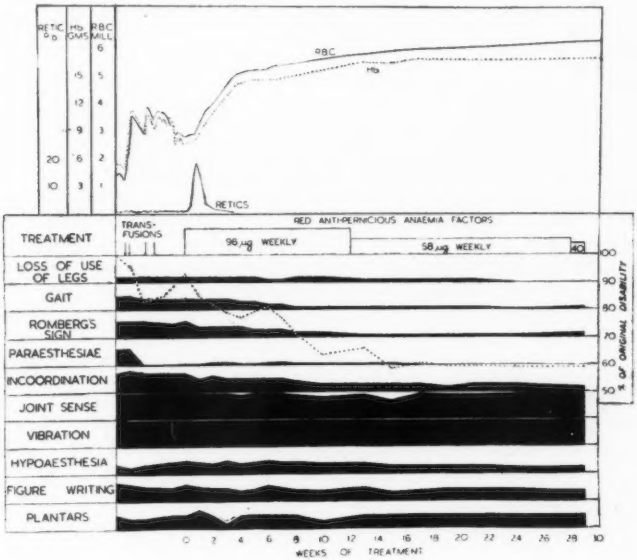

FIG. 13.—Case 47.

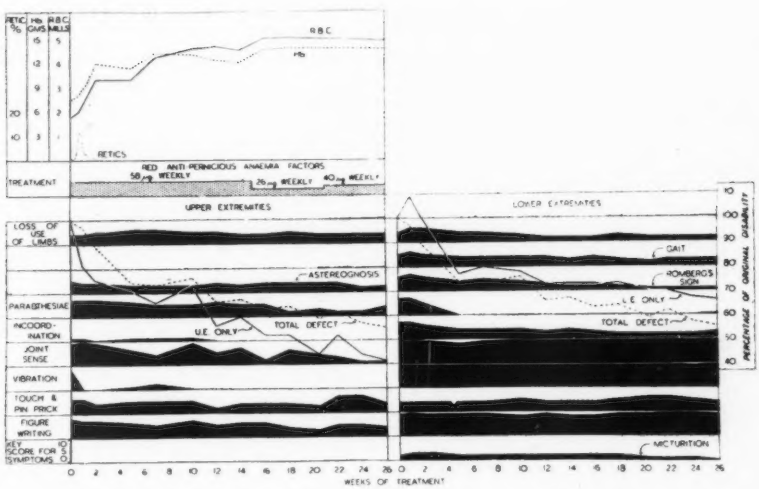

FIG. 14.—Case 48.

Comment.—The degree of improvement after treatment with red anti-pernicious anæmia factors was remarkable, considering the long duration of difficulty in walking.

Case 48 (A. M.), farm hand, aged 64, had anæmia, tingling and dysfunction of the hands for eight months, tingling in the feet, unsteadiness and precipitate micturition for two months.

Red pigmented material was given for twenty-one weeks; crystalline vitamin B_{12} thereafter (fig. 14).

Memory, initially defective for recent events, improved. He had optic atrophy with temporal pallor of the discs but no definite scotoma. Visual findings excluded an active tobacco amblyopia. For seven weeks the patient had to use a stick or touch furniture when walking except for short distances. At twelve weeks he walked many miles without help and at sixty-three weeks he walked nearly all day without a stick. At first the gait was very ataxic and he could not keep to a 15 cm. base. After eighteen weeks he could make a fair attempt at walking on a 7·5 cm. base. At sixty-three weeks he made 5 mistakes in 23 metres. For four weeks he overbalanced almost at once in Romberg's test, sometimes even before his eyes were closed. By twelve weeks improvement was definite and by twenty weeks he did not overbalance. Writing was poor, movements were clumsy and he had much difficulty in picking up pins; there has been little or no improvement. Difficulty in recognizing objects placed in the hand was considerable for twenty-two weeks (average score 4), less marked thereafter (average score 2·5).

Micturition was rather precipitate; after twenty-six weeks there was no trouble. Numbness and tingling receded from the mid-forearm to the fingers. Numbness receded from the knees to the toes. Inco-ordination of the upper limbs was very slight for the first twelve weeks. Inco-ordination of the lower limbs was moderately severe. Improvement was evident in five weeks. By sixty-three weeks the defect was slight. Joint sense in the fingers was markedly defective. Improvement was definite after the tenth week, and after twenty-six weeks the defect was slight. Joint sense remained absent in the toes. Vibration sense was absent up to and including the lumbar vertebræ. Improvement was gradual from twenty-six weeks onwards and after sixty-three weeks he could feel vibration in the lumbar spinous processes, in one ilium and in one patella. Sensory loss to touch and pin-prick in the hands and feet did not improve. The skin of the hands was thick and insensitive from farm work. Defective recognition of figure writing in the palms improved gradually, becoming slight at 33 to 63 weeks. Recognition remained defective in the soles. Power was normal. Tone was increased in the lower limbs. There was some general wasting. Except at the initial examination the calf muscles were not tender. Knee-jerks were normal. Ankle-jerks remained absent and plantar responses were flexor.

The total score diminished by 48 per cent in six months compared with the "expected" improvement of 53 per cent.

Comment.—In this moderately severe case improvement was slower but more prolonged than in some cases of equal duration. As commonly happens, the upper limbs improved rather more than the lower (*see* Part I).

Case 49 (E. J.), printers' labourer, aged 49, complained of pins and needles in the fingers for two months, and later in the feet so that he could not run.

He received red pigmented material for the first thirteen weeks and crystalline vitamin B_{12} thereafter. In tests for gait he walked on a broad base and made over 30 mistakes when pacing 23 metres on a 7·5 cm. line. Normality was reached in thirteen weeks. Later he was able to run. Paræsthesiæ in the fingers ceased at twenty-five weeks; in the feet they remained slight and variable. Slight inco-ordination of the lower limbs disappeared. Joint sense in the great toes remained

somewhat defective. Vibration sense, absent up to the lumbar vertebræ, improved in eight weeks and after seventeen weeks was usually normal or almost normal. Sensory loss to touch and pin-prick was insignificant. Defective recognition of figure writing in palms and soles became normal or practically normal. The reduction of 84 per cent in the total score compares with the "expected" 53 per cent; the reduction was slight in the first six weeks, rapid thereafter. From eleven weeks onwards symptoms and signs were minimal.

Comment.—This was a mild case with a short history. There was significant improvement in gait, vibration sense and figure writing, virtually complete at forty-two weeks. After thirteen months the state of arrest is maintained.

Case 50 (D. R.), a housewife, aged 59, had noticed dyspnœa at times for eight years, loss of weight for one year. The gait had been unsteady for two years, more so for three weeks.

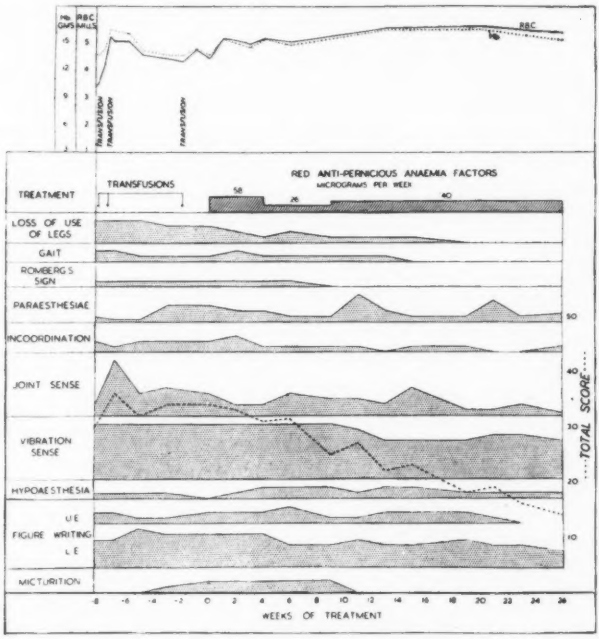

FIG. 15.—Case 50.

During the first eight weeks anæmia was controlled by blood transfusions. She received red pigmented material for nine weeks and thereafter crystalline vitamin B_{12} (fig. 15). Memory was somewhat defective for recent events (not assessed). The patient was unsteady and needed slight help at times. After nineteen weeks there was no difficulty. In attempting to walk 23 metres on a 7·5 cm. line the patient usually made about 10 mistakes. At fifteen weeks the gait was normal. In Romberg's test sway persisted until the sixth week. Slight difficulty in micturition developed in the control period and persisted until the ninth week of treatment. Numbness in the feet fluctuated both during the control period and under treatment; the changes were not considered significant. Slight inco-ordination of the lower

limbs persisted for twenty-one weeks. Defects in joint sense in the toes became very slight after nineteen weeks. Vibration sense was absent in the lower limbs, pelvis and lumbar vertebral spines. After the eleventh week vibration could be detected in some proximal areas. Defects in sensation to touch in the toes cleared up in thirty-two weeks. A slight defect in recognition of figure writing in the palms disappeared in twenty-three weeks. A severe defect in the soles disappeared in forty-six weeks. Knee-jerks were normal, ankle-jerks remained absent and plantar responses were flexor.

The total score, which had not altered in the control period, fell progressively during treatment. The observed reduction was 58 per cent, compared with the "expected" of 41 per cent. Up to fourteen months complete arrest is maintained.

Comment.—In this mild case relief of anæmia by transfusions did not lead to neurological improvement. The response to vitamin B_{12} was excellent considering that the duration of difficulty in walking was two years.

Case 51 (A. C.), a spinster, aged 63, had noticed numbness in the legs and hands, unsteadiness in walking and dysfunction of the hands for eight months.

She received crystalline vitamin B_{12} in the doses shown (fig. 16).

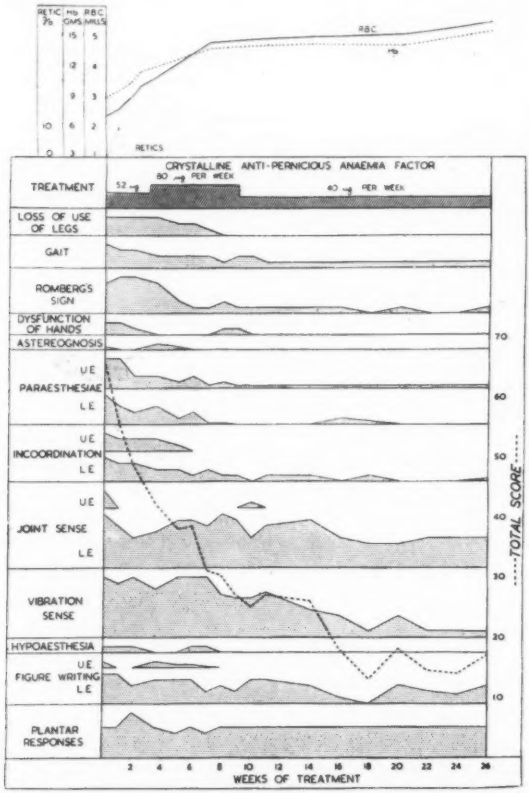

FIG. 16.—Case 51.

She was an intelligent and accurate witness with slight defect in memory for recent events. For the first month she needed slight help in walking at times. Then improvement was rapid and after two months there was no difficulty. At first she was unable to keep to a 7·5 cm. line. After eleven weeks the defect was very slight—usually about 7 mistakes in 23 metres. In Romberg's test she overbalanced in about fifteen seconds. After eight weeks there was no overbalancing and usually no sway. Slight difficulty in using the hands disappeared in fourteen weeks. Numbness involving the hands and the legs from knee to ankle was reduced to nil or a trace after seven or eight weeks. The mean error in the finger-nose test was 2 cm. Normality was reached in six weeks. There were moderate defects in heel-knee, sliding and localization tests. After eight weeks these defects were very slight or absent. Joint sense in the toes was grossly defective. After sixteen weeks the defect was moderate. Vibration sense, absent up to and including the lumbar vertebral spines, had improved by the eighth week and was almost normal at twenty-two weeks. Slight sensory loss to touch, mainly in the toes, disappeared in eight weeks. Recognition of figure writing was somewhat defective in the soles. Knee-jerks were normal, ankle-jerks remained absent and the left plantar response remained extensor. The observed reduction of 76 per cent in the total score compares with the "expected" improvement of 50 per cent.

Comment.—This patient, who had involvement of both upper and lower limbs of eight months' duration, improved rapidly. The almost complete recovery of vibration sense is unusual. Up to thirteen months the state of arrest is maintained.

Case 52 (J. A.), an air compressor attendant, aged 58, had anæmia, paræsthesiæ, dysfunction of the hands, and difficulty in walking for almost two years.

In the control period, during which anæmia was relieved by transfusion, walking deteriorated until he required help even for short distances. After twenty-six weeks' treatment with vitamin B_{12} he could walk a mile using a stick at times. In tests for gait he walked on a broad base and later needed strong support. After twenty-six weeks he walked alone on a 7·5 cm. line, making 19 mistakes in 23 metres. In the control period Rombergism increased so that he was unsteady even with eyes open and feet apart. After twenty-six weeks' treatment there was some sway but no overbalancing with heels together and eyes closed. Slight difficulty in finer movements of the hands disappeared in the control period. Slight precipitancy of micturition, noted in the last two weeks of the control period disappeared after five weeks. Paræsthesiæ in the finger ends have persisted. In the lower limbs pain and numbness extended up to the level of the umbilicus; after twenty-six weeks he had slight pain in the legs at times but no numbness or tingling. Inco-ordination of the lower limbs, which increased markedly during the control period, improved during treatment and the defect is now slight. Joint sense in the toes remained absent. Vibration sense remained absent to the level of the lumbar spine. Sensory loss to touch and pin-prick, mainly confined to the toes and distal sole, improved. Recognition of figure writing on the soles has not significantly improved. Tenderness of the calf muscles subsided to normal limits in nine weeks. Power was normal and there was no consistent abnormality in tone. Knee-jerks were normal. Active ankle-jerks, which became absent in the control period, returned in seventeen weeks and were normal at twenty-six weeks. The right plantar response was extensor. Later the left also was periodically extensor or equivocal, but the last four examinations have shown a right extensor and a left flexor response, as in the control period. The total score was reduced by 44 per cent, compared with the "expected" improvement of 41 per cent.

Comment.—During the control period anæmia was relieved by transfusion but the neurological condition relapsed. Because progress was

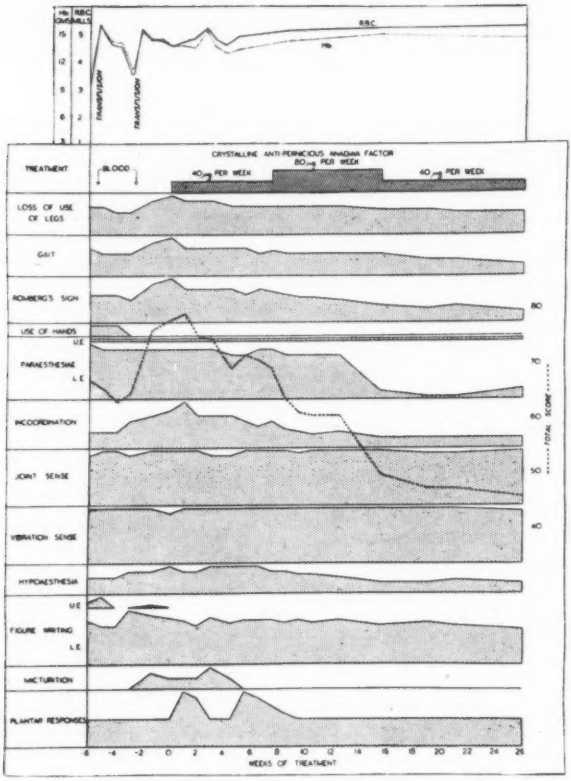

FIG. 17.—Case 52.

slow at first the dose of vitamin B_{12} was doubled. One cannot be certain, however, that the increased dosage was responsible for the more rapid improvement which followed.

Case 53 (M. J.), a widow, aged 65, had dyspnœa for five or six years, paræsthesiæ in the extremities for five months, difficulty in walking for three months, and recently a sore tongue.

Relief of anæmia by transfusion was not accompanied by neurological improvement. Partial amnesia for recent events disappeared during treatment with vitamin B_{12}. If well supported by two persons she could take a few steps, but the feet tended to slip from under her or to catch one behind the other. At four and a half weeks she walked across the ward with slight help and could climb back into bed. At seven weeks she took a few steps alone. After twenty-six weeks' treatment she could walk up and down stairs and about the house alone, and about 300 yards outside using a stick. In tests for gait she could place one foot in front of the other with difficulty if strongly supported on either side. At twenty-six weeks she walked unaided on a 7·5 cm. line making eleven mistakes in 23 metres and she could turn quickly without staggering. Even with feet apart and eyes open and with strong support on either side she could not keep her balance. After four and a half weeks she could just stand alone for a few seconds. At twenty-six

weeks she could stand alone with heels together and eyes closed with some sway but without overbalancing. Slight defects in finer movements and in the recognition of objects placed in the hand disappeared in eight to ten weeks. Moderate "pins and needles" involved the hands to the wrists. At twenty-six weeks there was very slight tingling in the finger ends. In the lower limbs moderate numbness extended up to the umbilicus. From the eleventh to twelfth week she was confined to bed for ten days with a febrile respiratory illness. Possibly as a result, paræsthesiæ, which at ten weeks had considerably diminished, increased to their former level. At twenty-six weeks she had moderate numbness in the toes and

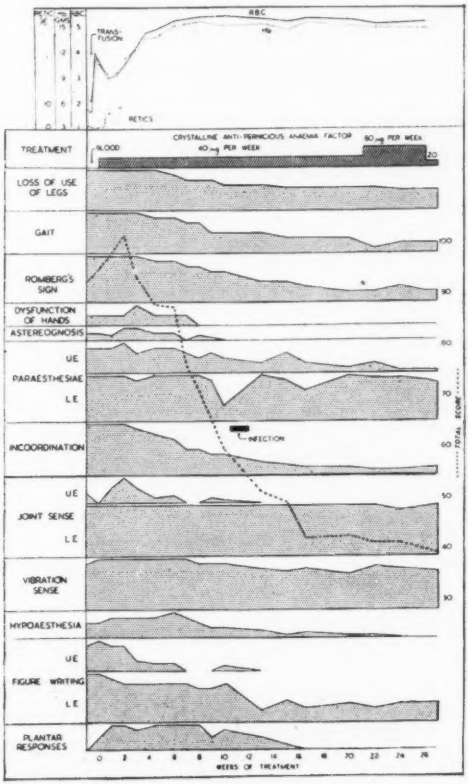

FIG. 18.—Case 53.

distal sole and between the knee and ankle, and transient numbness in the buttocks. Inco-ordination was severe: she missed the knee and toe completely, slid the heel down the bed in the sliding test, and missed by more than 12·5 cm. in localization tests. Improvement began after three weeks and by seventeen weeks inco-ordination was slight in all tests. Joint sense in the toes remained absent. Vibration sense was absent up to the first lumbar vertebræ; at twenty-six weeks it had returned to the lumbar vertebræ and to one ilium. Sensory loss to touch and pinprick over the toes, soles and ankles cleared up in twenty-four weeks. Moderately

defective recognition of figure writing on the palms improved and after the seventh week results were usually normal. Recognition was absent in the soles but improved during treatment. The calf muscles remained moderately tender throughout. Adductor tone was somewhat increased at first, later normal. Knee-jerks were normal. Ankle-jerks, particularly the right, were rather hyper-active, with ill-sustained clonus. Normality was attained in fifteen weeks. In the control period the right plantar response changed from flexor to equivocal, and for the first eight weeks of treatment it was extensor; after thirteen weeks' treatment it was again equivocal, at fifteen weeks probably flexor and from seventeen weeks onwards clearly flexor. The total score fell by 56 per cent compared with the "expected" response of 53 per cent.

Comment.—This severe case of short duration improved remarkably. The least responsive symptoms were paræsthesiæ, muscle tenderness and loss of vibration and joint sense.

Case 54 (A. F.), a housewife, aged 50, had difficulty in walking for five months, numbness and tightness in the legs for four weeks, and symptoms of anæmia.

She appeared somewhat depressed but there was no evidence of organic mental change and she proved to be a reliable witness. Relief of anæmia by transfusion was not accompanied by neurological improvement. She could take only a few

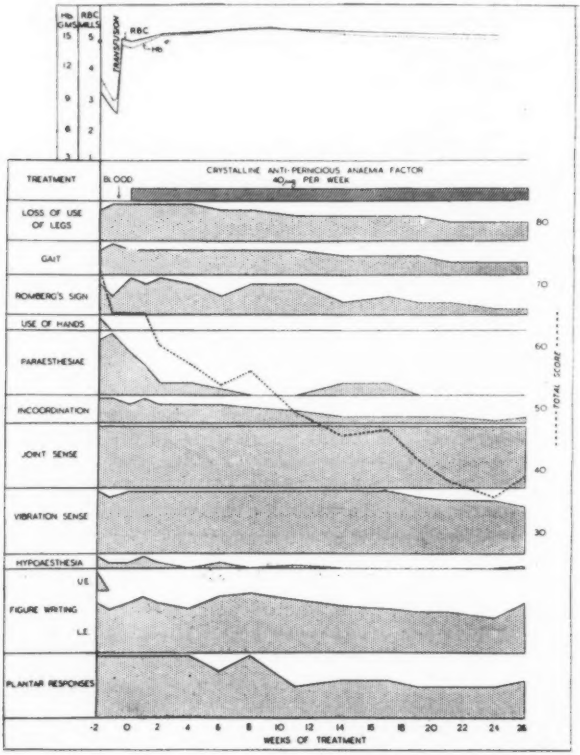

FIG. 19.—Case 54.

steps alone; inside the house she walked holding lightly on to furniture. After twenty-six weeks' treatment she walked outside alone, using a stick for long distances. She was unable to keep to a 7·5 cm. line. In twenty-six weeks she showed some improvement, making about ten mistakes in 23 metres. In Romberg's test she usually overbalanced in less than fifteen seconds. At twenty-four weeks there was slight sway but no overbalancing. Paræsthesiæ receded from the groins to the knees in the control period and disappeared completely during treatment. Slight to moderate inco-ordination of the lower limbs became very slight. Joint sense in the toes remained absent. Vibration sense, formerly absent in all test areas, showed a partial return in lumbar vertebræ and ilia. Sensory loss to touch and pin-prick was insignificant. Recognition of figure writing on the soles has shown no improvement. The calf muscles were occasionally tender at first. Power was normal. Tone in the lower limbs, particularly adductor tone, at first much increased, is now somewhat less. Knee-jerks remain exaggerated especially on the right side and are still obtainable down the front of the tibiæ. Patellar clonus is still present but no longer sustained. Hyperactive ankle-jerks have become normal. The left plantar response changed from extensor to flexor. The first change was at the sixth week, when the response was flexor from the inner border and equivocal from the outer. After the eleventh week the usual result was a clear-cut flexor response from both borders of the foot. The right plantar response remained extensor. During twenty-six weeks' treatment the total score has fallen by 46 per cent compared with the "expected" response of 52 per cent.

Comment.—In this case of short duration, paræsthesiæ, co-ordination and signs referable to involvement of the pyramidal tracts have improved.

Addendum.—In the five months elapsing since this paper was written neurological symptoms in the 8 patients receiving vitamin B_{12} have remained essentially unchanged. A 9th patient has now been treated long enough to assess progress. She had had severe difficulty in walking for 3½ months. In 36 weeks the total score has fallen from 100 to 38, an improvement of 62 per cent compared with the expected response of 53 per cent.

APPENDIX

Quantitative Method of Assessing Neurological Status

This method, which permits comparison of rates of improvement in patients or groups, has also been used in polyneuritis and immersion foot (Ungley, 1939, 1949*a*).

Examinations are carried out by the same physician (C. C. U.) while a third person acting as an observer records each fact as it is elicited without reference to previous findings. The question is not whether a symptom is better or worse than before, but what is its frequency, extent or severity now.

Emphasis has lain on recording facts rather than interpretations. Expressions of opinion, such as "marked", "moderate" or "slight" are replaced when possible by quantitative records, e.g. the number of mistakes in 20 tests for joint sense, the error in terms of distance during finger-nose tests, the number of selected points showing loss of vibration sense, or the number of arbitrary areas showing sensory loss to touch and pin-prick.

Errors are reduced by employing a standard technique, by repeating each test a number of times and by rest periods to limit fatigue.

Sensory tests are interspersed with examination of motor functions and reflexes or with enquiries about symptoms.

Since the knowledge of how one is doing is a factor in training (Macpherson,

Dees and Grindley, 1948) the patient is not told whether his answers are right or wrong.

Afterwards each symptom and sign is scored according to the scale. The sum of these scores gives the total score for neurological defect (*see* pp. 383 and 392).

When voluminous records of multiple tests are thus converted to numerical symbols, comparison of rates of improvement is simplified.

Sufficient data for the construction of satisfactory improvement curves can be obtained by the frequent examination of a small number of cases (every one or two weeks for the first six months—Part II) or by the less frequent examination of a larger number (Part I).

Before and during treatment certain essential signs, e.g. gait, Romberg's sign, inco-ordination, are recorded by cinematography.

Details of tests and scoring follow.

Loss of Use of Legs (Inability to Walk)

Scoring is based on the degree of inability to walk under everyday conditions.

Cannot move legs in bed	10
Can move legs but not take steps even if well supported ...	9
Able to take a few steps if well supported	8
Able to walk at least 15 metres if well supported	7
Able to walk a few steps alone or 15 metres with slight help, e.g. using stick or holding furniture	6
Able to walk at least 15 metres alone; inside house manages with occasional slight help; outside needs moderate help, e.g. an arm	5
Able to walk at least 50 metres alone, but normally uses a stick outside the house	4
Needs a stick or other slight help at times	3
Does not need a stick but is unsteady at times	2
Walking practically normal; or walks normally but cannot run	1

Gait

Until the patient is able to walk, the defect is graded as for "loss of use of legs." Thereafter he is asked to pace heel-to-toe five times along a line 7·5 cm. broad and 4·6 metres long. Scoring is based on the number of mistakes in 23 metres. A stagger in which both feet leave the line counts 2 mistakes; a sidestep in which one foot remains on the line scores 1, and an inaccurate step (foot not completely off the line) counts ½.

Walks at least 15 metres alone; unable to keep to 15 cm. base	5
Unable to keep to 7·5 cm. line; at least 30 mistakes in 23 metres	4
Makes 20 to 29 mistakes in 23 metres on a 7·5 cm. line ...	3
Slight defect on a 7·5 cm. line; 10 to 19 mistakes in 23 metres	2
Walks accurately but with difficulty on 7·5 cm. line; or makes 3 to 9 mistakes in 23 metres	1

By virtue of the overlap between "gait" and "loss of use of legs," difficulty in walking (usually the most incapacitating feature of the illness) is weighted more than other symptoms and signs in assessing the total neurological defect.

Inability to Stand (Including Romberg's Test)

Scoring is based on the mean of 3 tests.

Unable to stand even with help	10
Just able to stand if supported	9
Just able to stand alone with feet apart; unsteady even with eyes open	8
Just able to stand alone with feet together; unsteady even with eyes open	7

With feet together and eyes closed overbalances in 0 to 5 seconds	6
Overbalances in 6 to 15 seconds	5
Overbalances in 16 to 30 seconds	4
Overbalances in more than 30 seconds	3
Some sway but no overbalancing	2
Slight sway	1

As an additional measure some patients were asked to perform the finger-nose test at the same time (*see* Monrad-Krohn, 1948).

Difficulty in Using Hands

Difficulty in using the hands is assessed partly on the symptoms and partly on performance tests, which include writing and the picking up of pins.

	Each hand
Unable to use hands; cannot use spoon	5
Can use spoon, but not knife and fork	4
Cannot shave, write, knit or manage small buttons	3
Writing poor; difficulty with small buttons; cannot sew; movements clumsy	2
Slight defect in finer movements; drops things; difficulty in picking up pins	1

Recognition of Objects Placed in the Hand

Scoring is based on the *sum* of the marks obtained in the following categories:

	Each hand
Failure to recognize the presence of objects such as key or large coin, which may drop from the hand unknown to the patient	2
Failure to recognize the presence of a small coin, such as a sixpenny piece	1
Failure to detect the presence of cotton-wool	½
Failure to detect the presence of a pin	½
Incorrect designation of coins of different size, such as a penny and a halfpenny	½
Inability to distinguish between the shape of objects, such as a sixpenny piece and hexagonal threepenny piece	½

Paræsthesiæ

Paræsthesiæ were graded according to extent and severity.

		For each limb		
Upper limbs	*Lower limbs*	*Severe*	*Moderate*	*Slight or transient*
Upper arm or higher	Thigh or higher	5	4½	4
Elbow	Knee	4	3½	3
Wrist	Ankle	3	2½	2
Whole of fingers ..	Soles and toes ..	2	1½	1
Finger ends	Toes	1	½	(¼)

Inco-ordination

Upper limbs.—Scoring is based on the mean error of 10 finger-nose tests.

	Each hand
Misses tip of nose by 6·25 cm. or more	5
Misses tip of nose by 5·00 cm.	4
Misses tip of nose by 3·75 cm.	3
Misses tip of nose by 2·50 cm.	2
Misses tip of nose by 1·25 cm. or accurate but with tremor ...	1

Lower limbs.—Three different tests are used, all with the eyes shut.

(1) *Heel-knee-toe.*—The patient tries to place the heel first on the knee and then on the great toe of the other leg (five times). For severe inco-ordination the "Interposition test" is used. The heel is allowed to fall on to the hand of the examiner, who simultaneously exerts downward pressure on the heterolateral great toe. If the test is positive the patient believes that his heel is in place on the toe, even though they are in fact separated by several centimetres.

	Each leg
Misses by 12·5 cm. or more, or interposition test positive ...	5
Misses by 10 cm.	4
Misses by 7·5 cm.	3
Misses by 5·0 cm.	2
Misses by 2·5 cm. or accurate but with tremor	1

(2) *Sliding.*—The patient is instructed to slide the heel accurately five times down the shin from the knee to the ankle. In some instances a graphic record was obtained by placing over one leg a paper-covered board with a hole for the patella, the patient being asked to slide the other heel (previously dipped in charcoal) down the line of the shin.

	Each leg
Heel slides down the bed instead of on the shin	5
Heel slides down one or other side of the leg or slips completely off more than once, or slides down the bed for half the distance	4
Heel slips off altogether once, or partly off several times	3
Heel wavers down the shin or slips partly off once	2
Heel slides accurately but jerkily down the shin (slight defect) ...	1

(3) *Localization.*—The patient is asked to place the heel on the spot where he feels the physician's finger (10 different spots—mean error in centimetres).

	Each leg
Misses by 12·5 cm. or more	5
Misses by 10·0 cm.	4
Misses by 7·5 cm.	3
Misses by 5·0 cm.	2
Misses by 2·5 cm.	1

The score for inco-ordination of the limb is based on the mean of the scores obtained in the three tests described above.

Joint Sense

Joint position sense is tested in the proximal interphalangeal joint of the fifth finger and in the interphalangeal joint of the great toe. The end of the digit is included within the examiner's grasp in such a way that the additional pressure on one side involved by movement cannot easily be distinguished (Holmes, 1946). Standardized movements are made gently through a range somewhat short of the maximum, to avoid undue stretching or pressure; the patient, who is unable to see what happens, is asked to state whether the digit is bent or straight The tests are made according to a predetermined pattern, e.g.

First series: B.B.S.B.S.S.S.B.S.B.
Second series: B.S.B.S.S.S.B.S.B.B.
(when B = bent, and S = straight).

To avoid fatigue the two series are separated by an interval during which questions are asked about symptoms.

	Each side
Ten or more mistakes—complete loss	5
8 mistakes	4
6 mistakes	3
4 mistakes	2
2 mistakes	1

Vibration

Symns' fork (118 vibrations per second) is used. When disappearance of the "windows" indicates that the required amplitude has been reached, the instrument is applied in a standard manner over selected bony points, using "heavy" contact (equivalent to the weight of the fork, viz. 3·14 kg.). To detect unreliable witnesses who say they feel vibration when there is none, the fork is applied repeatedly, sometimes vibrating and sometimes still. Since false positives are less frequent when the patient neither sees nor hears the operation, his eyes are screened and his ears plugged, while the hum of the fork is drowned by extraneous noise (e.g. an electric fan).

The length of time patients could feel the vibration proved too inconstant a measure and we now rely on the extent of absolute loss.

One mark is scored for absolute loss over each of these points: medial malleoli, shins, patellæ, anterior superior iliac spines, sacrum, spine of second or third lumbar vertebra. Half a mark is scored for areas over which vibration is felt only faintly or inconstantly.

For example, the results in the right shin might be:

(i)	+	+	o*	+				(normal)
(ii)	o	o	o					(absent—score 1)
(iii)	o	sl	o*	sl	o	sl	o	(diminished—score ½)
or (iv)	+	+*	+	+*				(inconclusive—poor witness)

*Means that the fork was not vibrating.

Cutaneous Sensibility to Touch and Pin-prick

The limb is divided into small geometrical areas. The patient's face is screened and each area is touched in turn with a wisp of cotton-wool. A third person, acting as observer, records + or o in the appropriate square on the chart. Attention is checked from time to time, e.g. by touching an area of normal sensitivity, or by varying the time interval between stimuli. Later the areas are retested, in the reverse order, starting from the toes. In some individuals a relatively long interval between stimuli is necessary, otherwise the second stimulus evokes no response.

To obtain the score for the limb, the total number of anæsthetic areas (regions of partial loss counting as half) is divided by 10. For example, if there are 15 anæsthetic areas and 10 partially anæsthetic areas, the score is $(15 + 5) \div 10 = 2$.

Each area is likewise subjected to pin-prick. A response of "blunt" (meaning absence of pain sense) counts the same as no response.

The following table gives the equivalent of various scores in terms of area as complete sensory loss. In practice, of course, the sensory loss in some areas is partial rather than complete and the distribution is less perfectly geometrical than the table suggests.

	Number of areas (as complete loss)	Score for one limb
Under surface of toes	5	0·5
Whole of toes	10	1·0
Whole of plantar surface of foot	15	1·5
Whole of plantar surface of foot and dorsum of toes	20	2·0
Whole of foot and ankle	30	3·0
To top of knee	40	4·0
To top of thigh	50	5·0

Figure Writing

With the blunt end of a fountain pen figures approximately 5 cm. in height are drawn on the palm and the middle of the sole. The patient is informed that only certain numerals (1, 3, 8, 9 and 0) will be used. Scoring is based on the number of incorrect answers in 10 tests on each limb.

Reflexes

In subacute combined degeneration deep reflexes, power, tone and wasting in the extremities are excluded from the score (*see* p. 390).

Plantar responses, as elicited by stroking (*a*) the outer, and (*b*) the inner side of the sole, are recorded in the usual way: clearly extensor, probably extensor, equivocal, probably flexor, flexor.

Scoring on this basis can be used for following individual cases, but in the final analysis reliance is placed on the incidence of change from definite extensor to definite flexor.

Micturition

Incontinence or retention (constant)	10
Incontinence or retention (intermittent)	9
Marked disability*	8
Moderate disability: constant	6
Moderate disability: intermittent	4
Slight or occasional disability	2

*Disabilities include difficulty in performing or controlling micturition, slow starting, precipitancy or frequency. Severity is graded from marked to slight, according to the extent that the disability pervades the patient's consciousness and interferes with his mode of life.

Acknowledgments

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THE CROSS-SECTIONAL AREA OF PERIPHERAL NERVE TRUNKS DEVOTED TO NERVE FIBRES[1]

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INTRANEURAL funicular plexus formations lead to such rapid and extensive changes of the funicular pattern that destruction or resection, in the preparation of the nerve ends for suture, of more than a few millimetres of nerve can be expected to leave the opposing ends with dissimilar funicular patterns, the degree of dissimilarity depending on the length of the intervening gap (Sunderland, 1945*a*; Sunderland and Ray, 1948). It has also been shown that the funiculi are more compactly arranged in some regions than in others depending upon the looseness of the supporting epineurial framework and the amount of fat which it contains (Sunderland, 1945*b*). Thus despite a dissimilarity of the funicular patterns of the nerve ends, end-to-end apposition of funiculi may still be attainable during repair, and the chances of restoring useful connexions consequently improved, when the funiculi are tightly packed since there will then be less interfunicular tissue into which regenerating axons may be directed. The conditions, however, would be reversed when suture was performed in a zone where the funiculi were widely separated by an increased amount of interfunicular connective and/or adipose tissue. Under these circumstances the end-to-end apposition of funiculi would be rendered more difficult, or even impossible, and the possibility of some funiculi being unavoidably directed towards the interfunicular spaces would be considerable. When this occurs many regenerating axons would enter the interfunicular spaces and end blindly there. Recovery under such circumstances would be slower and less perfect and the prognosis consequently worse.

Thus, following suture of a severed nerve, the degree of separation of the bundles becomes a factor affecting the entry of regenerating axons into the endoneurial tubes of the funiculi of the distal stump and therefore a factor influencing the extent and quality of recovery. The separation depends on the size, number and arrangement of the component funiculi and on the amount of the interfunicular connective and adipose tissue. The investigation which forms the subject of this paper was undertaken to obtain this information for the radial, median, ulnar and sciatic nerves and to determine whether there were regional differ-

[1]This work was assisted by a grant from the National Health and Medical Research Council of Australia.

ences in this regard for each nerve or differences between individual nerves. For the purposes of the enquiry the degree of separation has been expressed in terms of the cross-sectional area of the entire nerve trunk occupied by the funiculi. The subject was briefly referred to elsewhere when reporting on the adipose tissue of peripheral nerves; subsequent studies have shown that the degree of separation of bundles is not determined alone by the amount of fat contained in the epineurium. The present report is not concerned with the factors which affect the restoration of the fibre-pattern but is concerned solely with the entry of regenerating axons into the funiculi.

Material and Methods

Observations were made on 20 specimens each of the radial, median, ulnar and sciatic nerves. Blocks of the median and ulnar nerves, approximately 1 cm. in length, were obtained at the following levels. The first was taken at the axillary outlet, the fifth at the medial epicondyle of the humerus and the last at the level of the tip of the styloid process of the radius. The second, third and fourth blocks were evenly spaced between the axilla and elbow. In the forearm two blocks were taken in one group and three in another; in each case these were evenly spaced between the elbow and the wrist. In the case of the median nerve the upper forearm block was taken just distal to the origin of the branches to the medial epicondylar muscle mass and the anterior interosseous nerve. Ulnar nerve sections were obtained above and below the origin of the posterior cutaneous nerve of the hand when three blocks were taken and just above this point when two blocks were taken. Blocks of the radial nerve were obtained at the axillary outlet, at the centre of the spiral groove, at the point where the nerve entered the furrow between the brachioradialis and brachialis muscles and just above the site of its terminal division into the superficial radial and posterior interosseous branches. Blocks of the sciatic nerve and its popliteal divisions were taken at the following six levels. The first was taken at the lower border of the piriformis muscle, the fifth at the level of the interval between the opposing surfaces of the femur and tibia and the sixth at the neck of the fibula. The second, third and fourth blocks were evenly spaced between the first and the fifth. Several specimens were selected in which there was a high division of the sciatic nerve so that its two popliteal divisions could be studied separately.

The blocks of tissue were submitted to a standard histological technique. They were fixed in formalin and embedded in paraffin. Transverse sections, 15 microns in thickness, were cut from each block and stained with hæmatoxylin and eosin. Material rendered unsatisfactory owing to shrinkage was discarded and a new series obtained. The sections were enlarged on a microprojector to a constant magnification and drawn. No difficulty was experienced in defining

the outer boundary of the nerve trunk. The cross-sectional area of the entire nerve trunk and the total cross-sectional area of the funiculi were then measured on the charts with a planimeter. At each level the cross-sectional area of the funiculi has been expressed as a percentage of the total cross-sectional area of the entire nerve trunk. Throughout the text the term "percentage cross-sectional area occupied by the funiculi" has been abbreviated to "percentage funicular area."

Observations and Discussion

(1) The number of funiculi and the area occupied by them at the different levels in each specimen investigated are given in Tables I to IV, while the average values for these two morphological features have been represented in graphic form in text figs. 1 to 5. In the tables the

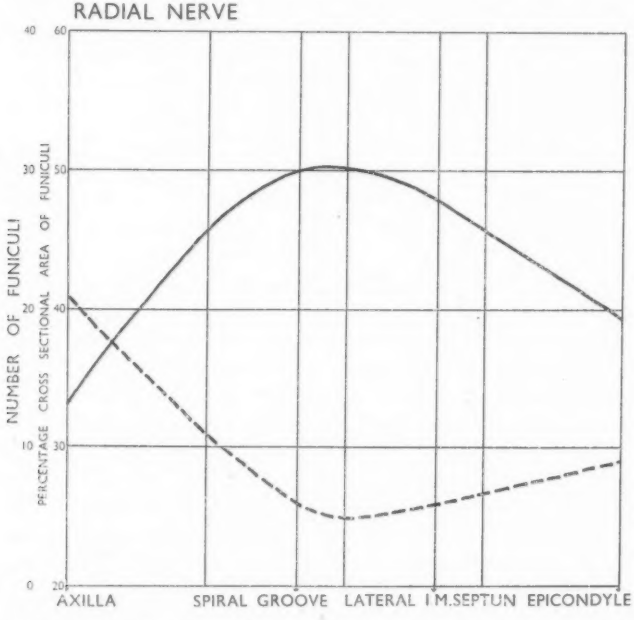

Fig. 1.—Graphic representation of the percentage funicular area (unbroken line) and number of funiculi (broken line) in the radial nerve. Lateral I.M. Septum = the point where the nerve leaves the bony spiral groove and enters the furrow between the brachialis and brachioradialis muscles.

specimens have been numbered according to the serial number of the subject from which they were obtained. This accounts for the rather peculiar notation used which was, however, employed so that if desired different nerves from the same subject might be compared. In constructing the graphs the values at each level were plotted as ordinates against the corresponding distances along the nerve as abscissæ. In

the case of the radial and popliteal nerves a smooth curve was drawn through the plotted points. In the case of the median and ulnar nerves eleven points were plotted in each since these two nerves were examined at quarter points in the upper arm but between the epicondyle and wrist

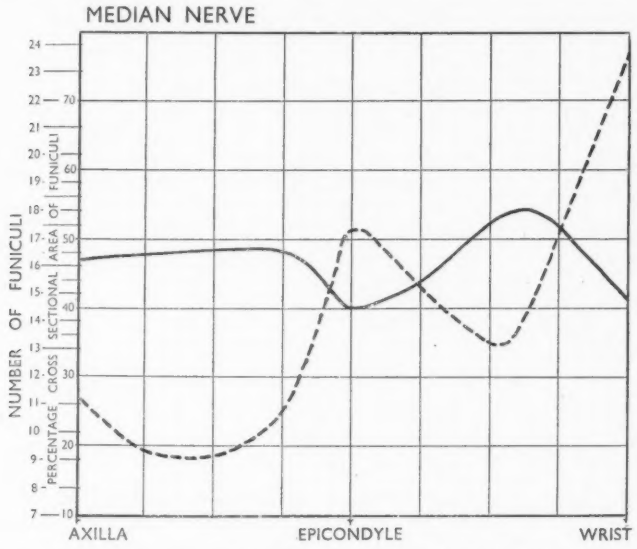

FIG. 2.—Graphic representation of the percentage funicular area (unbroken line) and number of funiculi (broken line) in the median nerve.

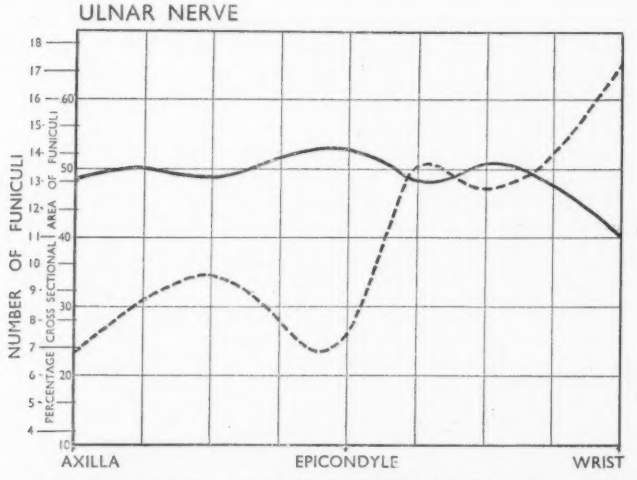

FIG. 3.—Graphic representation of the percentage funicular area (unbroken line) and number of funiculi (broken line) in the ulnar nerve.

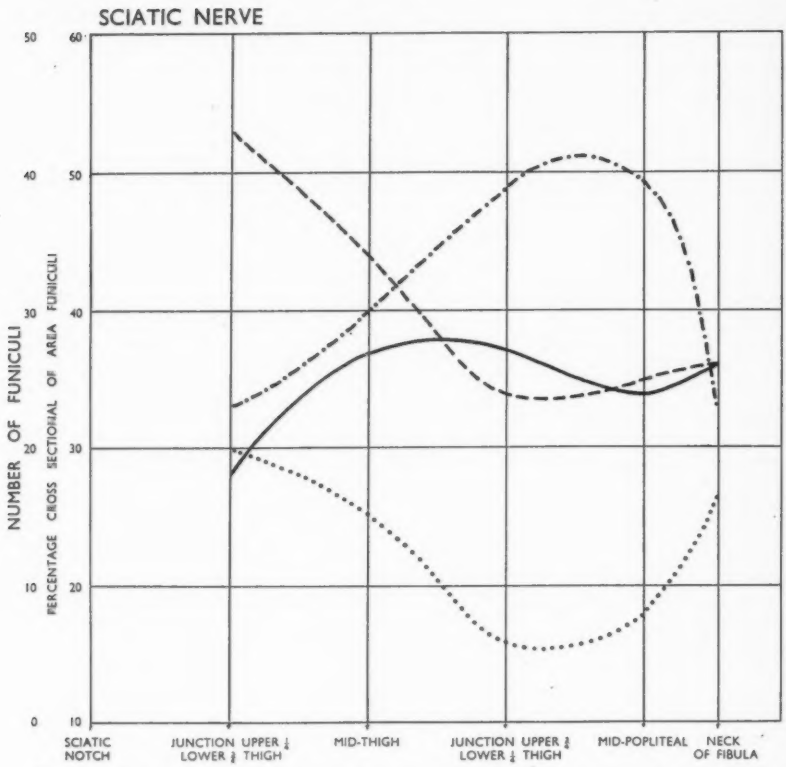

FIG. 4.—Graphic representation of the percentage funicular area and the number of funiculi in the popliteal divisions of the sciatic nerve. Medial division: Percentage funicular area, ——; Number of funiculi – – – –. Lateral division: Percentage funicular area, –·–·–·; Number of funiculi, ...

half the specimens were examined at quarter points and half at thirds. A smooth curve was drawn through the points above the epicondyle but below this level, since each plotted point represented an average of only half the specimens, a curve was drawn which most closely approximated to all the points plotted. The results of the investigation have shown that, at the levels investigated, the number of funiculi and the amount of the nerve occupied by them are subject to a wide range of variation. For this reason the graphs are only intended to show the average state of affairs at the levels investigated, but, considered as a whole, they do provide a fair representation of the manner in which the percentage funicular area changes along the length of each nerve and the manner in which it is inversely related to the number of funiculi at any level.

(2) Two outstanding features were: (i) The large amount of interfunicular connective tissue comprising a nerve trunk and the relatively

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Page 433. Section marked (4).

"70 per cent" *should read* "78 per cent".

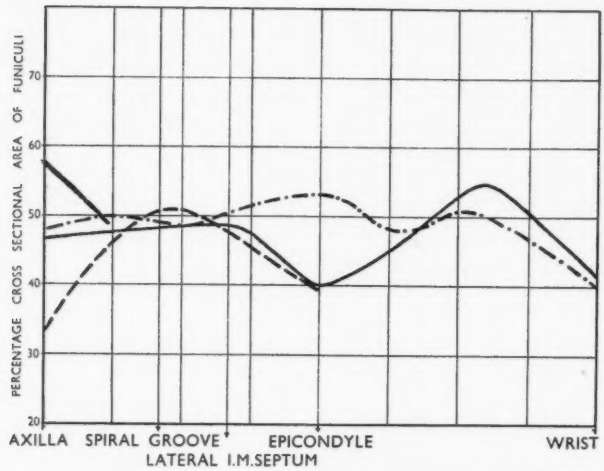

FIG. 5.—Comparison of the percentage funicular areas in the radial (– – – –), median (——), and ulnar (–·–·–) nerves.

small cross-sectional area occupied by the conducting elements. Though the amount of this packing ensures that the funiculi are well protected the conditions are such that the wasteful escape of regenerating axons into interfunicular spaces after end-to-end suture is inevitable.

(ii) The great variation in the percentage funicular area which fluctuated in an irregular manner from level to level along the same nerve and at corresponding levels on the two sides of the body, and from nerve to nerve and individual to individual. As a result the percentage funicular area is not necessarily identical at corresponding or any two levels (*a*) in the same nerve on opposite sides of the body so that the contralateral side may not offer control conditions, (*b*) in different nerves in the same individual, or (*c*) in the same and different nerves in different individuals. As a result only broad generalizations relating to this morphological feature are permissible.

(3) At any level the percentage funicular area varied inversely as the number of funiculi; the order of this variation was not constant.

(4) The highest percentage funicular area, namely 70 per cent, was observed in an ulnar nerve at the medial epicondyle and the lowest, namely 12 per cent, in a sciatic nerve at the sciatic notch. Both these values were exceptional.

(5) The average, highest and lowest percentage funicular areas for each peripheral nerve at each level where measurements were made, regardless of the particular specimen in which the reading was made, are given in Table V.

(6) The range of variation of the maximal and the minimal per-

centage funicular areas observed in each peripheral nerve (radial, median, ulnar and sciatic) based on the maximal and minimal reading for each specimen but regardless of the level providing the reading, is shown in Table VI.

From an analysis of the data provided in Tables I to VI it may be concluded that:

(i) The average, the highest and the lowest values respectively for the maximal and minimal cross-sectional area measurements were substantially the same for each nerve except the medial popliteal where all three values for the maximal reading were much lower.

(ii) The greatest percentage funicular area will rarely exceed 50 per cent in the medial popliteal nerve and 70 per cent in the remainder. It is more likely to be in the vicinity of 40 to 50 per cent in the radial and medial popliteal nerves and 50 to 65 in the remainder.

(iii) There are specimens in which the greatest contribution of the funiculi to the cross-sectional area may be as low as 40 to 50 per cent, or in the case of the medial popliteal nerve, even as low as 24 per cent.

(iv) Somewhere along each nerve the percentage funicular area will reach minimal values of, on the average, 27 to 36 per cent while there

TABLE I.—THE RADIAL NERVE

The number of funiculi and the percentage cross-sectional area of the nerve trunk occupied by them at various levels. At each level the value for the funicular area precedes the number of funiculi.

Subject *R = right side* *L = left side*	*Axillary outlet*	*Spiral groove (excluding the posterior cutaneous of the forearm)*	*Level where the nerve enters the furrow between the brachialis and brachioradialis muscles*	*At the elbow immediately proximal to the site of terminal division*
1L	41/29	53/5	45/8	45/10
2R	23/32	30/10	39/3	40/3
3L	27/21	50/4	32/12	16/9
4R	23/19	63/2	71/2	32/6
5L	47/13	42/12	53/7	30/12
6L	30/20	70/1	48/3	41/11
7L	51/2	70/1	63/1	46/3
8R	24/20	53/4	51/4	50/9
9R	34/13	61/2	54/2	48/7
10L	29/18	49/7	46/7	45/12
11R	24/28	49/3	48/2	32/10
11L	29/36	71/2	46/10	47/9
12R	44/13	44/3	45/6	40/10
12L	30/11	41/3	40/2	46/4
13R	30/32	44/9	44/9	34/10
13L	31/22	32/8	40/12	30/13
14R	30/29	41/8	47/10	39/16
14L	39/27	55/7	46/4	57/3
15R	39/17	45/13	63/4	39/9
15L	41/16	47/9	43/9	33/8

TABLE II.—THE MEDIAN NERVE

The number of funiculi and the percentage cross-sectional area of the nerve trunk occupied by them at various levels. At each level the value for the funicular area precedes the number of funiculi. Lat. H and Med. H = lateral and medial head of the median nerve.

Subject	*Axillary outlet*	*Junction of upper $\frac{1}{4}$ and lower $\frac{3}{4}$ of arm*	*Mid-arm*	*Junction of upper $\frac{3}{4}$ and lower $\frac{1}{4}$ of arm*	*Epicondyle*	*Junction of upper $\frac{1}{4}$ and lower $\frac{3}{4}$ of forearm*	*Mid-forearm*	*Junction of upper $\frac{3}{4}$ and lower $\frac{1}{4}$ of forearm*	*Wrist*
11R	38/10	40/7	42/6	41/9	27/16	43/6	48/10	54/6	52/11
11L	40/14	41/7	43/11	40/5	42/14	41/9	38/5	53/12	49/16
12L	49/3	45/5	49/7	53/4	42/16	39/18	49/10	56/7	50/15
16R	41/14	44/10	47/7	39/11	32/17	33/14	41/18	46/13	25/28
16L	65/3	32/13	45/9	45/12	43/14	37/20	52/9	43/15	32/22
17R	57/15	37/13	36/11	45/13	33/22	48/20	48/24	33/27	36/35
17L	39/19	61/7	54/8	45/12	34/17	41/20	48/21	45/26	33/37
18R	62/6	51/11	48/7	48/7	48/12	48/12	58/7	54/7	28/24
18L	56/10	44/4	62/3	49/4	43/8	48/6	59/7	46/9	30/19
19R Lat. H	52/1	62/1	46/5	33/8	33/7	33/20	48/10	33/12	35/37
Med. H	46/2	61/1							

Subject	*Axillary outlet*	*Junction of upper $\frac{1}{4}$ and lower $\frac{3}{4}$ of arm*	*Mid-arm*	*Junction of upper $\frac{3}{4}$ and lower $\frac{1}{4}$ of arm*	*Epicondyle*	*Junction of upper $\frac{1}{3}$ and lower $\frac{2}{3}$ of forearm*	*Junction of upper $\frac{2}{3}$ and lower $\frac{1}{3}$ of forearm*	*Wrist*
5L	44/17	63/11	50/11	52/14	52/27	40/19	59/22	49/27
9R	46/11	49/10	61/5	59/7	31/16	54/14	58/10	43/20
10L	28/13	51/15	37/13	51/15	38/25	66/11	71/14	45/20
13R	35/15	42/15	46/26	42/25	31/29	41/19	47/33	44/36
13L	57/18	42/21	40/14	47/26	34/28	33/27	48/23	42/35
14R	46/9	54/10	58/9	52/11	45/16	48/16	67/13	49/23
14L	49/5	43/5	60/15	62/5	48/18	53/15	57/22	37/28
15R	41/18	52/10	48/3	65/6	47/15	56/9	68/9	55/18
15L	51/10	47/5	55/9	49/14	51/14	62/15	64/13	31/20
20R	42/13	60/5	47/6	52/9	41/14	58/4	68/12	70/6

TABLE III.—THE ULNAR NERVE

The number of funiculi and the percentage cross-sectional area of the nerve trunk occupied by them at various levels. At each level the value for the funicular area precedes the number of funiculi.

Subject	*Axillary outlet*	*Junction of upper ¼ and lower ¾ of arm*	*Mid-arm*	*Junction of upper ¾ and lower ¼ of arm*	*Epicondyle*	*Mid-forearm*	*Junction of upper ¼ and lower ¾ of forearm*	*Junction of upper ¾ and lower ¼ of forearm*	*Wrist*
1R	55/8	51/7	58/6	65/6	44/8	43/19	50/20	49/16	**38/13**
2L	38/5	51/4	61/6	53/10	53/6	38/17	41/13	38/12	**35/27**
3L	63/1	64/2	39/6	56/5	69/1	52/8	54/7	44/16	**21/21**
11R	62/1	42/7	59/4	46/7	58/2	46/18	52/11	52/12	**29/11**
12L	48/8	39/10	52/10	54/7	56/7	51/13	58/10	50/7	**41/18**
16R	51/9	54/7	42/10	50/8	58/8	42/17	56/17	40/15	**34/14**
21R	33/15	42/6	38/15	38/7	54/5	53/12	50/10	46/25	**39/19**
22R	34/6	36/11	30/13	31/16	40/7	48/13	53/9	44/15	**31/12**
22L	49/8	57/7	40/12	43/5	45/12	31/11	47/13	54/7	**41/17**
23L	70/1	52/6	53/7	46/9	63/4	35/6	49/11	55/10	**43/18**

Subject	*Axillary outlet*	*Junction of upper ¼ and lower ¾ of arm*	*Mid-arm*	*Junction of upper ¾ and lower ¼ of arm*	*Epicondyle*	*Junction of upper ¼ and lower ¾ of forearm*	*Junction of upper ¾ and lower ¼ of forearm*	*Wrist*
4R	51/4	45/7	59/5	48/6	51/5	57/10	48/9	31/14
5R	35/7	51/4	52/7	52/1	52/6	61/5	59/3	55/8
5L	54/5	53/12	53/12	63/10	54/11	57/14	51/18	49/20
10L	60/4	43/9	60/12	55/7	59/5	54/11	61/10	51/20
13R	29/14	42/19	40/20	55/12	39/20	37/23	37/22	26/36
13L	27/20	30/26	49/17	43/20	44/15	35/26	35/30	47/13
14R	53/6	53/9	50/10	56/7	58/11	59/17	46/12	49/18
14L	48/4	48/8	43/7	65/8	43/9	58/20	47/16	51/19
15R	59/6	57/5	45/11	58/3	41/4	52/11	55/14	51/12
15L	52/5	46/8	54/5	61/4	78/2	48/9	57/8	53/17

TABLE IV.—THE SCIATIC NERVE

The number of funiculi and the percentage cross-sectional area of the nerve trunk occupied by them at various levels. At each level the value for the funicular area precedes the number of funiculi. M and L = medial and lateral popliteal divisions respectively.

Subject	*Sciatic notch*		*Junction upper ¼ and lower ¾ of thigh*		*Mid-thigh*		*Junction upper ¾ and lower ¼ of thigh*		*Mid-popliteal*		*Neck of fibula*	
	M.	L.	M.	L.	M.	L.	M.	L.	M.	L.	M.	L.
5R	29/56	34/22	42/39	52/15	48/36	50/11	51/19	56/4	50/19	49/10	39/34	28/24
24R	31/48	39/19	35/38	33/15	36/32	38/11	35/20	46/8	32/36	43/15	35/26	35/24
25R	15/32	16/11	17/33	19/9	17/31	32/12	22/25	20/9	24/16	70/1	18/23	25/14
4R	22/51		19/27	22/18	30/13	47/20	43/11	47/4	34/16	50/5	38/20	40/10
5L	28/92		34/41	43/21	45/32	43/15	42/30	52/4	43/16	65/1	38/24	37/16
9R	17/62		26/36	45/16	46/32	43/13	46/18	53/4	36/17	38/6	42/21	36/13
13R	21/137		24/83	29/31	37/52	36/23	34/36	46/12	36/32	46/6	24/48	40/14
13L	24/136		22/93	29/36	37/59	33/34	22/47	39/7	24/54	28/27	41/28	30/17
14R	27/65		29/33	31/16	37/36	37/11	41/28	54/8	33/25	61/6	42/22	32/21
14L	25/54		37/25	40/25	41/27	51/6	47/17	60/4	39/20	63/4	47/21	30/21
25L	12/42		18/25	21/15	28/27	30/13	28/17	70/1	21/23	24/6	31/19	18/11
26L	26/80		24/49	21/22	20/62	29/17	22/67		28/32	57/10	30/29	34/22
27L	24/57		24/54		28/48	28/29	37/34	32/15	31/29	53/4	41/32	18/25
28L	24/64		28/63		32/33	42/11	32/16	46/3	42/14	52/5	37/17	41/14
8R	23/58		31/41		37/44		39/22	33/12	40/29	50/4	33/30	36/17
8L	40/53		31/42		41/33		34/23	58/8	42/26	45/8	39/25	40/24
20L	24/42		34/51		32/45		57/18		48/17	48/10	37/20	32/14
26R	25/70		14/62		25/68		21/55		36/40	47/11	28/33	25/27
29L	26/61		30/55		26/61		32/41		38/34	44/6	26/26	24/19
30R	24/47		28/38		32/44		40/36		35/14	49/5	38/21	28/17

TABLE V.—THE AVERAGE, HIGHEST AND LOWEST PERCENTAGE FUNICULAR AREAS FOR EACH PERIPHERAL NERVE REGARDLESS OF THE PARTICULAR SPECIMEN IN WHICH THE READING WAS MADE

	LEVEL										
Nerve	*Axillary outlet*	*Junction upper $\frac{1}{4}$ and lower $\frac{3}{4}$ of arm*	*Mid-arm*	*Junction upper $\frac{3}{4}$ and lower $\frac{1}{4}$ of arm*	*Medial humeral epicondyle*	*Junction upper $\frac{1}{4}$ and lower $\frac{3}{4}$ of forearm*	*Junction upper $\frac{1}{3}$ and lower $\frac{2}{3}$ of forearm*	*Mid-forearm*	*Junction upper $\frac{2}{3}$ and lower $\frac{1}{3}$ of forearm*	*Junction upper $\frac{3}{4}$ and lower $\frac{1}{4}$ of forearm*	*Wrist*
Radial..	51/33/23		71/50/30	71/48/32	57/39/16						
Median	65/47/28	63/48/32	62/49/36	65/48/33	52/40/27	48/41/33	66/51/33	59/49/38	71/61/47	56/46/33	70/42/25
Ulnar	70/49/27	64/50/30	61/49/30	65/52/31	78/53/39	53/44/31	61/52/35	58/51/41	61/50/35	55/47/38	55/41/21

	Sciatic notch	*Junction upper $\frac{1}{4}$ and lower $\frac{3}{4}$ of thigh*	*Mid-thigh*	*Junction upper $\frac{3}{4}$ and lower $\frac{1}{4}$ of thigh*	*Mid-popliteal*	*Neck of fibula*
Sciatic..	40/24/12					
Medial popliteal ..		42/28/17	48/37/17	51/37/22	50/34/21	47/36/18
Lateral popliteal ..		52/33/19	51/40/30	70/49/20	70/49/24	40/32/18

TABLE VI

Nerve	*Maximal percentage funicular area*			*Minimal percentage funicular area*		
	Average	*Highest reading*	*Lowest reading*	*Average*	*Highest reading*	*Lowest reading*
Radial	54	71	40	31	46	16
Median	60	71	47	34	45	25
Ulnar	61	78	49	36	49	21
Medial popliteal	40	51	24	27	39	17
Lateral popliteal	56	70	39	28	37	18

are occasions when at some levels the funiculi may occupy as little as 16 to 25 per cent of the nerve.

(v) The funiculi in the medial popliteal nerve are more loosely arranged than in other nerves.

(7) The difference between the highest and lowest readings for the percentage funicular area in each specimen may be accepted as a measure of the full extent of the change in this morphological feature occurring along the length of the nerve. Such information, based on data provided from the full series of specimens investigated, is provided in Table VII.

TABLE VII

Nerve	*Average of the differences between the maximal and minimal percentage funicular area*	*Highest reading for the differences between the maximal and minimal percentage funicular area*	*Lowest reading for the differences between the maximal and minimal percentage funicular area*
Radial	23	48	5
Median	27	43	15
Ulnar	25	48	13
Medial popliteal	13	24	4
Lateral popliteal	28	52	11

The variation in the percentage funicular area along the medial popliteal nerve is unlikely to exceed 24 per cent but in the remainder it may be as high as 40 to 50 per cent. On the other hand, the variation may be as low as 5 per cent for the radial and medial popliteal nerves and 10 to 15 per cent in the remainder. However, the average values for the various nerves were substantially the same (23 to 28 per cent) except for the medial popliteal where a lower average (13 per cent) obtained.

(8) An analysis of the information contained in Tables I to IV relating to the number of funiculi and the percentage area occupied by them permits the following generalizations for each nerve.

RADIAL NERVE

The greatest percentage funicular area recorded for each level in any specimen was the same for the spiral groove and the level immediately

distal to it (71 per cent); the maximal readings for the axilla and elbow were 51 to 57 per cent respectively. The lowest areas recorded for the series were for the elbow (16 per cent) and axilla (23 per cent); the values for the remaining levels were substantially the same (30 and 32 per cent).

A comparison of the percentage funicular areas at different levels in the same individual.—In the majority of specimens the percentage funicular area was greatest either in the spiral groove or at the point where the nerve passed anterior to the lateral intermuscular septum, the incidence slightly favouring the former level; in 3 specimens the area at the elbow was the maximal but by values of only 1, 2 and 5 per cent. In no instance was the maximal area observed in the axilla. The lowest area in each specimen was usually observed in the axilla, frequently at the elbow but at no other level.

A comparison of the percentage funicular areas at different levels in different individuals.—The range of variation of the percentage funicular areas is such that, though in any individual the area in the spiral groove or just beyond it will be maximal for that particular nerve, these values will not necessarily exceed those obtaining in the axilla and at the elbow in other individuals though the observations suggest that in general this will be the case.

The nerve was composed of a large number of bundles in the axilla which were rapidly reduced in the spiral groove where, in half the specimens, the number varied from 1 to 4. Distal to the groove the funiculi increased in number as far as the elbow where, however, they were not nearly as numerous as in the axilla except in one specimen in which the numbers at the four levels were, from proximal to distal, 2, 1, 1 and 3. The number of funiculi in the axillary section of any specimen usually exceeds the numbers at more distal levels in other specimens.

Median Nerve

The greatest percentage funicular area observed at each level, regardless of the specimen in which it occurred, was about the same (60 to 70 per cent) except at the elbow, mid-forearm and at the junction of the upper one-fourth and lower three-fourths and of the upper three-fourths and lower one-fourth of the forearm at which four levels lower maximal readings (50 to 60 per cent) were recorded. At each level the lowest area recorded was about the same (25 to 35 per cent) except at the junction of the upper two-thirds and lower one-third of the forearm where a higher reading was obtained.

A comparison of the percentage funicular areas at different levels in the same individual.—In any specimen the greatest percentage funicular area will be found either (*a*) in the proximal three-fourths of the upper arm or (*b*) in the vicinity of the upper two-thirds and lower one-third of the forearm though the latter site is usually favoured. The only exception was provided by one specimen in which the area at the wrist was superior and then by only 2 per cent. This, however, was an

unusual specimen in that the nerve was composed of a solitary bundle at the wrist; sections at this level in over 200 specimens had not previously revealed such an arrangement.

The lowest percentage funicular area for each specimen was usually recorded either at the elbow or wrist. Exceptions were provided by 3 specimens in which it was observed above the medial humeral epicondyle.

A comparison of the percentage funicular areas at different levels in different individuals.—The variation in the funicular areas was such that it was difficult to effect a comparison between the conditions obtaining at different levels in different individuals. However, in any group of individuals the percentage funicular area at the elbow and wrist in one will be less than that in the upper arm, at the mid-forearm and at the junction of the upper two-thirds and lower one-third of the forearm in most of the others.

The number of funiculi at each level varied greatly from specimen to specimen though the variation became more marked at distal levels. Thus the numbers ranged from 3 to 15 at the mid-upper arm (excluding one exceptional case) and from 15 to 37 at the wrist (excluding two cases where the funicular counts were 6 and 11). In general there was a progressive increase in the number of funiculi as the limb was descended. There was, however, a consistent reduction in the numbers just below the mid-forearm, though this was not sufficient to reduce the counts below the values observed in the proximal part of the upper arm. The number of bundles at the wrist in one individual will, with very few exceptions, exceed the number in the axilla in any other.

Ulnar Nerve

The greatest percentage funicular area observed at each level, regardless of the specimen in which it occurred, was as follows: axilla (70), epicondyle (78), levels between the axilla and epicondyle (61 to 65), the third points in the forearm (61), mid-forearm (58) and the remaining forearm levels and the wrist (53 to 55).

The lowest percentage funicular area recorded for each level was: wrist (21), above the elbow and at the junction of the upper one-fourth and lower three-fourths of the forearm (27 to 31) and at the elbow and the remaining forearm levels (35 to 41).

A comparison of the percentage funicular areas at different levels in the same individual.—The greatest percentage funicular area may be found anywhere between the axilla and the mid-forearm though the favoured site is the epicondyle and the region just above it. The lowest areas were rarely found below the mid-upper arm except at the wrist where the incidence of the lowest readings was highest.

A comparison of the percentage funicular areas at different levels in different individuals.—It was difficult to effect a useful comparison owing to the wide variation in the percentage funicular areas. How-

ever, there is a suggestion that the area at and just above the epicondyle will usually exceed that at other levels and that the area at the wrist in one individual will be lower than at other levels in others.

In individual specimens the number of bundles gradually increased from the axilla to the mid-upper arm and then gradually diminished as far as the epicondyle, beyond which the number progressively increased as far as the wrist though there was a minor reduction at the mid-forearm.

The number of bundles at corresponding levels in different specimens was subject to a wide range of variation which became more marked as the arm was descended. Thus in the axilla the numbers ranged from 1 to 9 in all but 3 specimens in which values of 14, 15 and 20 were recorded. At the wrist the numbers ranged between 11 and 27 in all but 2 cases. With few exceptions the number at the wrist would exceed that in the axilla.

Sciatic Nerve

The percentage funicular area at the sciatic notch did not show the same wide variation as was observed in the other nerves and, in general, was much lower in value. The greatest and lowest areas measured were 40 and 12 per cent respectively though these were exceptional values. In 14 of the 20 specimens the values ranged from 21 to 28 per cent.

The range of the percentage funicular area over the 6 specimens in which the two divisions of the sciatic nerve were fused as far as the mid-thigh was: for the junction of the upper three-fourths and lower one-fourth 14 to 34 per cent and for the mid-thigh 25 to 41 per cent.

The poor recoveries recorded after suture of the sciatic nerve in the buttock and in the proximal half of the thigh could be attributed, in varying but considerable measure, to the low percentage funicular areas obtaining in these regions.

Lateral Popliteal Division

The maximal percentage funicular area recorded for each level in the specimens investigated was greatest at the junction of the upper three-fourths and lower one-fourth of the thigh and the mid-popliteal level (70 per cent), lowest at the neck of the fibula (40 per cent) and intermediate in value at the remaining levels (52 and 51 per cent). The lowest areas recorded for each level were substantially the same at the junction of the upper one-fourth and lower three-fourths, and of the upper three-fourths and lower one-fourth of the thigh and at the neck of the fibula (19, 20 and 18 per cent respectively) while slightly higher readings were recorded at mid-thigh (30 per cent) and mid-popliteal (24 per cent) levels.

A comparison of the percentage funicular areas at different levels in the same individual.—The site of the greatest percentage funicular area was divided equally between the mid-popliteal level and the junction of the upper three-fourths and lower one-fourth of the thigh; in

no case was it observed at any other level. The lowest area was situated either at the neck of the fibula or at the junction of the upper one-fourth and lower three-fourths of the thigh though in one specimen the area at the mid-popliteal level was the lowest by 2 per cent.

A comparison of the percentage funicular areas at different levels in different individuals.—No level consistently showed a greater area than the others though in one individual the area at the junction of the upper three-fourths and lower one-fourth of the thigh will usually exceed that at the neck of the fibula in others.

The funiculi were least numerous at the junction of the upper three-fourths and lower one-fourth of the thigh and at the mid-popliteal level where the numbers in any specimen rarely exceeded those at the remaining levels in others.

Medial Popliteal Division

The greatest percentage funicular area recorded for each level was substantially the same in the various specimens (42 to 51 per cent) as was the lowest area (17 to 22 per cent).

A comparison of the percentage funicular areas at different levels in the same nerve.—The greatest area was not observed at the junction of the upper one-fourth and lower three-fourths of the thigh, where the lowest readings were recorded, and very rarely at the mid-popliteal level. The greatest area was distributed over the remaining levels though less frequently at the neck of the fibula than elsewhere.

A comparison of the percentage funicular areas at different levels in different individuals.—Owing to the irregular fluctuations in the percentage funicular areas it was not possible to effect a useful comparison in this regard.

In individual specimens the funiculi were most numerous at the highest level in the thigh; the number was slightly less at the mid-thigh beyond which there was a sharp reduction so that the counts at the remaining levels were much lower than those at more proximal levels though they were of substantially the same order for each of the lower levels. In different individuals the number at the distal three levels was usually less than that at the proximal two levels.

(9) The various peripheral nerves may be arranged in the following order of merit, as regards the favourability of local conditions for repair on the basis of (1) the percentage funicular area and (2) the number of funiculi. When the former is high and the latter low, the arrangement favours the entry of regenerating axons into funiculi of the distal stump following end-to-end suture. On the other hand, when the area is low and the number high the arrangement favours the escape and wasteful regeneration of axons into interfunicular spaces. It is to be noted, however, that these are only two of several morphological features influencing the extent and quality of recovery after suture.

On the basis of the percentage funicular area.—(i) Radial nerve in

the spiral groove and at the point where it enters the furrow between the brachialis and brachioradialis muscles. Ulnar nerve as far distally as the lower fourth of the forearm. Median nerve in the proximal three-fourths of the upper arm and in the vicinity of the upper two-thirds and lower one-third of the forearm. Lateral popliteal nerve in the lower fourth of the thigh as far distally as the mid-popliteal level.

(ii) Radial nerve at the elbow. Median and ulnar nerves in the lower fourth of the forearm and the median nerve at the elbow. Lateral popliteal nerve at the mid-thigh.

(iii) Radial nerve in the axilla. Lateral popliteal nerve at the neck of the fibula and in the proximal half of the thigh. Medial popliteal nerve as far distally as the knee.

(iv) Sciatic nerve in the buttock.

On the basis of the number of funiculi.—(i) Radial nerve in and below the spiral groove. Median nerve in the axilla and in the proximal three-fourths of the upper arm. Ulnar nerve at and above the elbow. Lateral popliteal nerve in the lower fourth of the thigh as far distally as the mid-popliteal level.

(ii) Median nerve at and below the elbow but excluding the wrist. Ulnar nerve in the forearm but excluding the elbow and wrist.

(iii) Radial nerve in the axilla. Ulnar nerve at the wrist. Remainder of the lateral popliteal nerve.

(iv) Median nerve at the wrist. Medial popliteal nerve in the distal half of the thigh.

(v) Sciatic nerve in the buttock. Medial popliteal nerve in the proximal half of the thigh.

(10) A. Zones in each nerve where the two morphological features under review combine to render the conditions unfavourable for recovery after repair are :

Radial nerve : at the axilla and elbow.
Median nerve : at the elbow and wrist.
Ulnar nerve : at the wrist.
Medial popliteal nerve : in the proximal half of the thigh.
Lateral popliteal nerve : in the proximal half of the thigh and below the mid-popliteal level.
Sciatic nerve : in the buttock.

B. Zones in each nerve where the arrangement is more favourable, though not necessarily good, for recovery after end-to-end suture. The qualification "though not necessarily good" is added because even when the percentage funicular area is maximal there will still be sufficient interfunicular connective tissue to result in the wasteful escape of some regenerating axons into the interfunicular spaces particularly when there is any dissimilarity in the funicular patterns of the opposed nerve ends.

Radial nerve : in the spiral groove and at the level where the nerve enters the furrow between the brachialis and brachio-radialis muscles.

Median nerve : in the vicinity of the upper two-thirds and lower one-third of the forearm ; proximal three-fourths of the upper arm.

Ulnar nerve : as far as the distal fourth of the forearm.

Medial popliteal nerve : in the distal half of the thigh.

Lateral popliteal nerve : in the lower fourth of the thigh as far distally as the mid-popliteal level.

(11) In general the funiculi were more closely packed in the lateral than in the medial popliteal nerve. It is conceivable that the reduced amount of protective connective tissue packing in the former may contribute to the greater susceptibility to injury of this devision of the sciatic nerve.

(12) When comparing the end-results of suture at the same and different levels in the same (i.e. radial) and different (e.g. radial and median) nerves, consideration should be given to the percentage funicular area at the level of repair since this is a factor influencing the wasteful regeneration of axons into the interfunicular spaces and, in this way, the extent and quality of the recovery. Owing to the variability of this morphological feature, the data furnished by this enquiry can be expected to provide only an approximate estimate of the funicular area at any particular level in a peripheral nerve which is not available for examination. In order, therefore, to ascertain the *precise* conditions obtaining at the site of repair, sections of the proximal and distal stumps should be taken when the nerve ends are being prepared for union and submitted to cross-sectional analysis. The information thereby obtained would be of value in determining the possible influence of this factor on the usefulness of regeneration and in this way would provide a guide to prognosis. Such information is also essential for the proper evaluation of the various factors influencing recovery and for the correct assessment of the value of any modification of treatment or technique, such as, for example, the influence on the course of recovery of the time interval between injury and repair and the relative merits of various suture materials.

(13) *On the trimming of nerve ends in preparation of end-to-end suture.*—When preparing nerve ends for suture the practice is to trim them carefully until "healthy bundles" or "satisfactory cross sections" are exposed. The terms "healthy" and "satisfactory," however, remain undefined while the term "healthy" is somewhat confusing in that the faces of the opposing nerve ends are unlikely to present the same appearance because of the degenerative changes that take place below the lesion. From a survey of the literature on this subject these two terms are presumably used to apply to a condition in which there is an absence of fibrous thickening, with the funiculi clearly visible and

filling the nerve, with a minimal amount of intraneural connective tissue which is loose in texture and soft in consistency, with the funiculi of the proximal face showing the appearance that is characteristic of cut normal funiculi, and with the exposed surface bleeding freely. The concept that this is the only normal arrangement and therefore the one to be carefully sought when preparing nerve ends for union is misleading in some respects. As a result of the observations made in this investigation relating to the amount (as opposed to the density) of the intraneural connective tissue together with the number, arrangement and degree of separation of the funiculi, all of which are subject to a wide range of normal variation, great caution must be exercised when examining the trimmed surfaces of the nerve ends to decide when morphological conditions are optimal for union. Failure to appreciate and recognize this range of normal variation introduces the danger of unnecessarily resecting normal tissue in an attempt to obtain an arrangement which the nerve does not normally show in that region. This point is mentioned because it is felt that the cross-sectional picture of a large amount of supporting connective tissue with a few widely separated bundles may be regarded as pathological and the trimming consequently unnecessarily extended in the expectation of exposing a larger number of bundles with less interfunicular tissue. The quality of the connective tissue and the appearance presented by the exposed face of each funiculus in the proximal stump, and not the number and the compactness of the bundles, are the reliable features when assessing the suitability of the nerve end for repair.

Unnecessary trimming of nerve ends can be prejudicial to recovery first by increasing the distance between the nerve ends, which should be kept to a minimum so that the measures required to close the gap and permit end-to-end union will not result in harmful tension at the suture site, and secondly by increasing the length of nerve destroyed. The thesis will be developed elsewhere that the most mischievous factors militating against recovery are those that foster the wasteful regeneration of axons into the interfunicular spaces and these are introduced when there is a dissimilarity of the funicular patterns of the opposing nerve faces. This dissimilarity is increased as the length of nerve destroyed or removed in the surgical resection increases and for this reason every attempt should be made to conserve nerve tissue when preparing the nerve ends for repair.

(14) The escape of regenerating axons into the interfunicular spaces is considerably increased when the funicular area is small. Under these circumstances the separate suture of bundle groups representing individual branches, as advocated by Langley (1918), has the advantage of reducing this loss. This, however, is not practicable in some regions for technical reasons and because of the absence of any significant branch bundle group localization which prevents the accurate identification and isolation of bundles representing individual branches. However,

funicular suture does appear to be a practical proposition in certain regions. This subject will be discussed in detail in a subsequent report.

Summary

(1) The number of funiculi and the percentage cross-sectional area of the nerve trunk occupied by them have been calculated at several levels in 20 specimens each of the radial, median, ulnar and sciatic nerves.

(2) An outstanding feature was the large amount of interfunicular connective tissue comprising the nerve trunk. Though the amount of this packing ensures that the funiculi are well protected, conditions are such that the wasteful escape of regenerating axons into interfunicular spaces after end-to-end suture is inevitable.

(3) The percentage funicular area varied greatly and in an irregular manner from level to level along the same nerve and at corresponding levels on the two sides of the body and from nerve to nerve and individual to individual.

(4) At any level the percentage funicular area varied inversely as the number of funiculi.

(5) The highest percentage funicular area, namely 75 per cent, was observed in an ulnar nerve at the medial humeral epicondyle and the lowest, namely 12 per cent, in a sciatic nerve at the sciatic notch; both these values were exceptional.

(6) The greatest percentage funicular area observed along the length of the nerve will rarely exceed 50 per cent in the medial popliteal and 70 per cent in the remainder. It is more likely to be in the vicinity of 40 to 50 per cent in the radial and medial popliteal nerves and 50 to 65 per cent in the remainder. There are specimens, however, in which the greatest contribution of the funiculi to the cross-sectional area may be as low as 40 to 50 per cent, or, in the case of the medial popliteal nerve, even as low as 24 per cent.

(7) Somewhere along each nerve the percentage funicular area will reach minimal values of, on the average, 27 to 36 per cent while there are occasions when at some levels the funiculi may occupy as little as 16 to 25 per cent of the nerve.

(8) The percentage funicular area for the sciatic nerve at the sciatic notch did not show the same wide variation as was observed in the other nerves and, in general, was much lower in value. The greatest and lowest areas measured were 40 and 12 per cent respectively though these were exceptional values. In 14 of the 20 specimens the values ranged from 21 to 28 per cent.

When the two divisions of the sciatic nerve were fused as far as the mid-thigh the funicular area ranged from 14 to 34 per cent at the junction of the upper three-fourths and lower one-fourth of the thigh and from 25 to 41 per cent at the mid-thigh.

The poor recoveries reported after suture of the sciatic nerve in the buttock and in the proximal half of the thigh could be attributed, in

varying but considerable measure, to the low percentage funicular areas obtaining in these regions.

(9) Details relating to the percentage funicular area along individual nerves are provided together with the results of comparisons of this value at different levels in the same and different individuals.

(10) The manner in which the number of funiculi and the percentage cross-sectional area of the nerve occupied by them influence the extent and quality of the recovery after end-to-end suture has been discussed. When the funicular area is low and the number of bundles high, the wasteful escape of regenerating axons into the interfunicular spaces is favoured while the converse obtains when the funicular area is high and the bundles few in number. In this connexion the investigation has revealed significant regional differences as regards these two morphological features in peripheral nerves; these have been described.

(11) The various peripheral nerves have been compared on the basis of the two morphological features under review and on the findings have been arranged in order of merit as regards the favourability of local conditions for repair.

(12) Zones in each nerve where the conditions are unfavourable for recovery after repair are:

Radial nerve: at the axilla and elbow.
Median nerve: at the elbow and wrist.
Ulnar nerve: at the wrist.
Medial popliteal nerve: in the proximal half of the thigh.
Lateral popliteal nerve: in the proximal half of the thigh and below the mid-popliteal level.
Sciatic nerve: in the buttock.

(13) Zones in each nerve where the conditions are more favourable though not necessarily good, for recovery after repair are:

Radial nerve: in the spiral groove and at the level where the nerve enters the furrow between the brachialis and brachioradialis muscles.
Median nerve: in the vicinity of the upper two-thirds and lower one-third of the forearm; proximal three-fourths of the upper arm.
Ulnar nerve: as far as the distal fourth of the forearm.
Medial popliteal nerve: in the distal half of the thigh.
Lateral popliteal nerve: in the lower fourth of the thigh as far distally as the mid-popliteal level.

(14) The importance of a knowledge of the percentage cross-sectional area of nerve trunks devoted to funiculi has been discussed in connexion with:

(i) The necessity of obtaining cross-sections from the nerve ends at the time of repair and of submitting this biopsy material to cross-sectional analysis. Information obtained in this way would be of value in ascertaining the possible influence of the factors under review on the

usefulness of regeneration, and in this way would provide a guide to prognosis. Such information is also essential for the proper evaluation on the basis of end-result assessments of the various factors influencing recovery and for the correct assessment of the value of any modification of treatment or technique.

(ii) The trimming of nerve ends in preparation for end-to-end suture.

(iii) The funicular suture of peripheral nerves.

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THE SPONTANEOUS ELECTRICAL ACTIVITY OF THE HUMAN THALAMUS

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THE spontaneous electrical activity of the human brain has so far been recorded from the scalp (the electro-encephalogram) from the exposed cortex (electro-corticogram) and from the neighbourhood of subcortical tumours. There is very close similarity between records made of the electrical changes passing through electrodes placed on the scalp and on the cortex, the main difference being that the changes found in the scalp have a lower voltage. The similarity has been so close that there has been general agreement that the electro-encephalogram can give a fairly accurate idea of the potential differences between the two areas of the cortex underlying the two electrodes on the scalp.

In view of the changes which have been found in the electro-encephalogram of subjects with deep tumours, with disturbances of the basal ganglia, and of the structures around the third ventricle, and also in view of the theories which have been presented to explain the abnormal electrical rhythms seen in epilepsy, there has been speculation upon the relationship between the activity of the basal grey matter and the apparently spontaneous electrical activity of the cerebral cortex. This cortical activity has been very extensively studied in every normal and abnormal state from all accessible areas of the cortex, and indeed the relative simplicity of the technique has encouraged this prospecting. Cortical activity has also been examined in less accessible areas by means of special electrodes such as those which are placed upon the mucosa of the nasopharynx (Grinker, 1938; Roubicek and Hill, 1948), and in the tympanic region (Arellano, 1949), while Walter and Dovey (1946) have shown that changes similar to those recorded from the scalp can be found around subcortical tumours.

Animal experiment has shown that suitable electrical stimulation of the basal ganglia will modify the electrical activity of the cortex and indeed Lewy and Gammon (1940) and Jasper and Droogleever-Fortuyn (1947) found that stimulation of the cat's thalamus caused rhythmic discharges in the cerebral cortex similar to the "wave and spike" complexes of human epilepsy. In consequence of these observations the

current physiological idea of reverberating circuits has been applied to the discharges of epilepsy, the view being that rhythmic cortical activity might be initiated and maintained by electrical discharges from the basal structures. In support of this view have been the observations of Dusser de Barenne and McCulloch (1936) and others that isolation of cortical areas from the basal ganglia by subcortical section of white matter has altered the pattern of the cortical rhythm, but on the other hand Gerard and Libet (1939) found that poikilothermic cortex (which may not be comparable with that of mammals) continues to discharge rhythmically when isolated *in vitro* in the same way as it does in the intact animal.

There has been clinical evidence, mainly derived from lesions in the neighbourhood of the thalamus and third ventricle (Walter, Griffiths and Nevin, 1939; Cairns, Oldfield, Pennybacker and Whitteridge, 1941) and which includes personal unpublished observations, which indicates that lesions confined to the basal structures cause the appearance of very slow waves throughout the cortex with suppression or modification of the normal rhythms. Furthermore, rhythms of a special frequency (4–7 per second) have been recorded from the scalp in patients with deep tumours, and it has been concluded that they result from damage to the thalamus or neighbouring structures.

As most of the evidence from man was indirect and much of the reasoning inductive, we decided to record the electrical activity of the surface grey matter, the basal grey matter and the intervening white matter simultaneously by direct implantation of electrodes into their substance. After a suitable apparatus and technique had been evolved and tested, records were made at the same time as electro-encephalograms, electrocardiograms and other observations in normal subjects, in those with different gross lesions of the cerebral hemispheres, and in conditions such as coma, akinesis, and epilepsy. This paper deals with the method and with some of the results obtained.

Method.—The subjects of the investigations were all patients in the Neurological or Neurosurgical Departments of St. George's Hospital. We are indebted to Mr. Wylie McKissock for access to the surgical patients and to their notes. The patients all required ventriculography for which parieto-occipital burr holes were made in the usual way by members of the neurosurgical staff. The special thalamic electrode was introduced and records obtained either before or more usually a few days after the brain needle was inserted for the introduction of air into the ventricle. Because this work was entirely experimental, and because the decision to advise burr holes cannot be undertaken lightly, the work had to be limited to patients in whom there was suspicion of a gross intracranial lesion. It has consequently been impossible to include absolutely normal subjects, although there have been some whose electro-encephalograms were normal and who were subsequently found to have a normal ventricular system. Such was the case in one of the patients whose epileptic fits were later found to be due to spontaneous hypoglycæmia. This limitation is a serious one, for we believe that the conditions existing in normal subjects should be known before abnormals are studied.

As the surgeon's brain needle which is introduced as a routine for ventriculography seems to do no evident damage to the brain, the electrodes we were to introduce enclosed in such a needle should not do so either. Surgeons had often been noticed to "overshoot" the ventricle and so presumably to penetrate the basal ganglia without any immediate or delayed effect upon the patient, so that again it seemed that our needle electrodes could be introduced without ill-effects if their shape was that of a brain needle, and if they were introduced in the same manner as a brain needle. Because of these important considerations the electrodes were actually enclosed in a brain needle, and the whole instrument was sterilized and introduced by a surgeon, using the technique of ventriculography. We are particularly grateful to Mr. K. Till for having helped us so often in this way.

Material.—So far 27 successful experiments have been carried out on 22 patients, the procedure having been repeated in 5 cases. As each experiment was a major undertaking, patients were carefully selected, mainly upon the nature of their disorder, so that different forms of epilepsy and various positions and kinds of gross lesions were selected. The conditions studied have included the following:

- Normal
- Epilepsy
  - Idiopathic
    - Grand mal
    - Psychomotor
    - Petit mal
  - Symptomatic
    - General
      - Grand mal
      - Psychomotor
    - Focal
- Cerebral Lesions
  - Superficial
    - Tumours
      - Frontal
      - Temporal
      - Parietal
    - Cortical atrophy
    - Large cyst
  - Deep
    - Thalamic tumour
    - Third ventricular syndrome

The patients' ages ranged from 5 to 65 and all except one were alert. Sleep was induced in some with intravenous pentothal, and various experimental changes, which included changes in blood pH and sugar, the introduction of painful stimuli, alteration of attention, and mental exercise, were used.

Procedure.—The patients lay with their heads supported on sandbags, insulated upon an earthed trolley in an earthed and insulated cage. The electrodes encased in the brain needle were introduced by a member of the neurosurgical staff in such a way that the tip of the needle seemed to be in the basal grey matter, and it was fixed in place by sterile gauze dressings and elastoplast, the fine wires leading to the electro-encephalogram protruding through the dressing. These

wires led to the input of three independent amplifying circuits. Simultaneously electro-encephalograms were recorded from the scalp in the ordinary way upon two recording channels, and an electrocardiogram and sometimes a record of the respiration upon the remaining channel of the Grass electro-encephalogram.

During the recording the patient lay still and any changes—whether produced by the patient or by the experimental situation—were noted in the records. After the experiment radiograms were taken of the skull with the needle and electrodes *in situ*, the position of the needle and electrodes being the same as in the ventriculogram. In the early experiments air was still present in the ventricles, so that the positioning of the electrodes within the brain could be accurately established by direct contrast (fig. 4). If this were not the case superimposition of the bony outline of the ventriculogram plates and those with the needle shown in position achieved the same result (figs. 1, 3, 6, 7, 8, 12).

It was usually our aim to have one pair of recording electrodes in the thalamus, the next in the white matter over it, and a third in or near the cerebral cortex. An electrode in the scalp just beside the point of exit of the needle was used with the "cortical" electrode to record from cortex to scalp, and a fifth simultaneous recording was made across the scalp, over the burr hole. There was consequently a chain of electrodes picking up simultaneous electrical changes in a line from the thalamus, ventricle, white matter, cortex and scalp as well as others recording changes produced by the heart and respiration. Records were made with several different combinations to the inputs of the amplifiers including "unipolar" recording in which each of the four deep electrodes was paired with a relatively indifferent ear electrode. Experience showed that "bipolar" recording between serial pairs of electrodes up the length of the needle produced the maximal contrast between the records from each position. It had two great advantages (1) that cortical potential changes from the so-called indifferent electrode did not obscure the records, and (2) that comparison of contiguous records, particularly when phase reversals were present, led to accurate localization. This second advantage was increased by obtaining further records after the needle had been withdrawn 0·5 or 1·0 cm. at a time. In this way the changes in the form, amplitude and phase relationship of waves could be used in localization along the depth of the needle track.

Electrodes.—Basically the technique was that of routine electro-encephalography, which need not be described. The intracerebral electrode consisted of a standard silver brain needle, in which small holes had been drilled on one side at the tip, and at intervals of 2, 4 and 6 cm. from the tip. Four strands of 22 gauge copper wire enamelled and doubled silk covered were run down the lumen of the needle to emerge at the centre of each hole. The whole needle was then filled and coated with Bergers' Hymeg No. 1 insulating varnish. The emerging points of the wire were exposed, polished and then silver chlorided. The wires after emerging from the needle were fused to thicker flexible insulated copper wire, that from each point having a distinctive colour. These needles can be autoclaved or subjected to chemical antiseptics. The final form of the needles was the result of several trials, technical difficulties being found in achieving perfect insulation between the fine wires within the lumen, in having the emerging leads to the input light and flexible as well as durable, and in constructing an insulated needle which could be sterilized. All the trial needles and the ones finally used were made by Mr. H. B. Morton of the National Hospital, Queen Square.

As the needle is insulated, there are in fact four point electrodes consisting of the ends of the wires, surrounded by an insulated metal shield. Comparison of records obtained through these electrodes with those from large scalp electrodes showed that they were in similar circumstances identical. The four electrodes were connected in serial pairs to the amplifier inputs in the usual way. The scalp electrodes were solder pledgets with Cambridge electrode jelly.

A difficulty which arises in recording in this way is that an electrode—usually

that 2 cm. from the tip—is in the cerebrospinal fluid of the ventricle. As will be seen later this causes a phase reversal at that electrode, which we could not at first explain since other signals, such as those produced by alternating potential changes induced elsewhere in the body, were always in phase through the four electrodes. We subsequently found that this was due to a pulse artifact.

Results

An example of each of the main groups of conditions studied will be presented with an outline of the clinical facts, diagrams of the electrode positions, sample of the E.E.G. and representative portions of the intracerebral recording. They are in order:

Case 1	Normal	Left hemisphere
Case 1	Tumour	Occipital
Case 2		Temporal
Case 3		Parietal
Case 4		Frontal
Case 5		Thalamic
Case 6	Cortical atrophy	
Case 7	Epilepsy	Idiopathic
Case 8		Symptomatic
Case 9		Reflex
Case 10		Mixed
Case 11		Psychopath

Normal

Case 1.—*Normal left hemisphere:* As the technique of thalamic recording cannot be undertaken in a normal subject we have studied patients who, though abnormal in other regards, had a normal E.E.G. When a local lesion was confined to one hemisphere, and the E.E.G. records from the other hemisphere were normal, thalamic records were obtained from that normal side, in default of records from entirely normal people. Case No. 107447, described later as an example of abnormality in the thalamus and in the cortex as a result of a right occipital tumour, was used in this way, for the patient was fully alert and co-operative, her behaviour was quite normal, there was no rise in intracranial pressure, and the evidences of the occipital tumour were entirely local. Furthermore, the E.E.G. was normal from all areas on the left side. In this case, records were made from the cortex and the thalamus on both sides simultaneously. Those from the normal left side may be contrasted with the abnormal right and are shown in figs. 1 and 2. The abnormal records obtained on the right side are described later.

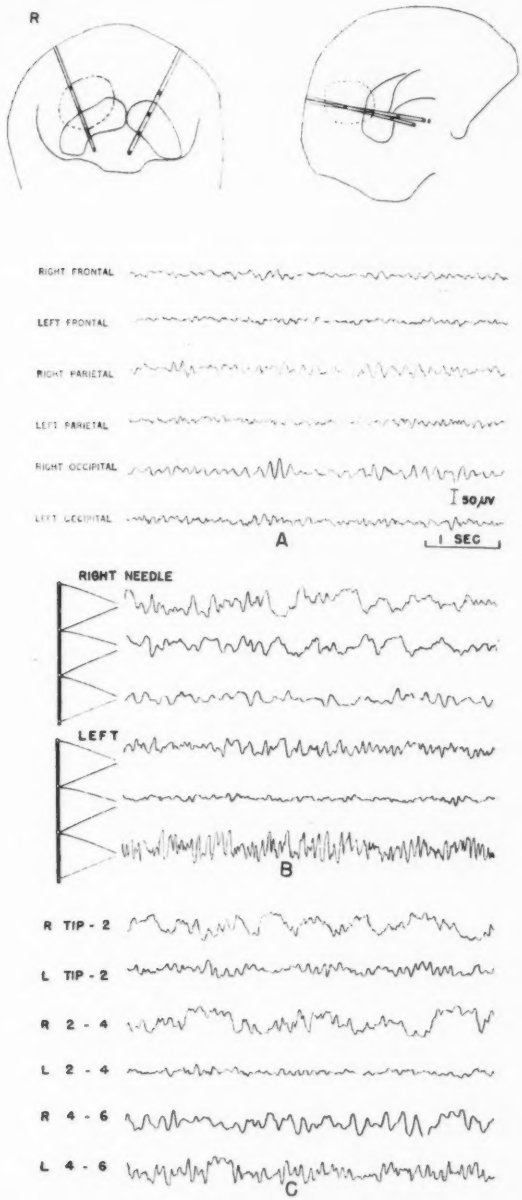


FIG. 1 (*See* legend p. 480).

The normal records showed a stable dominant frequency of 9 a second arising in the left parieto-occipital area. It had a relatively high voltage and attenuated in a normal manner with passage forwards.

When the needle electrodes were initially inserted the depth of the needle tip from the scalp was 8 cm. and in this position a 9 a second rhythm, identical with that obtained from the top pair of electrodes, was recorded from the needle tip. The voltage of this frequency in the middle pair was much attenuated (fig. 2D). On withdrawing the needle 1 cm. the 9 a second rhythm recorded from the tip attenuated greatly but the two more superficial pairs of electrodes showed a rhythm of higher voltage with a clearly marked phase reversal between them (fig. 2E). When the needle was withdrawn a further 1·5 cm. the voltage of the records remained similar to that of the previous recording but the 9 a second rhythm was more obvious in the deep lead (fig. 2F). No abnormal waves of any sort complicated the superficial records and no rhythms other than the 9 a second were recorded from the deeper structures. These serial records suggested that the 9 a second rhythm recorded initially from the needle tip arose from the subjacent temporal cortex. This being so the overlying basal grey matter seemed to have contributed nothing to the pattern of the electrographic records. This observation was repeated in other cases.

Cortical Lesions: Tumours

Case 1.—*Occipital tumour:* Hospital Case No. 107447. Female, aged 66. Admitted 9.11.48. For nine years the patient had migraine in which the visual symptoms were always on the left. Three years before one of these attacks was complicated by focal epileptic movements involving the left arm and leg. Later she had two major convulsions, and more recently severe headache and mental confusion. She was a frail woman who was alert and co-operative. She had a complete left homonymous hemianopia and a mild hemiplegia involving mainly the arm.

Electro-encephalogram (10.11.48) showed continuous rhythmic 6 a second waves occurring in the right parieto-occipital region (fig. 1A). The normal dominant frequency was 10 a second.

Ventriculogram (12.11.48): Both ventricles were encountered at a depth of 6 cm. through posterior parietal burr holes. The septum pellucidum was displaced 0·4 cm. to the left. The lateral ventricles were dilated and measured 2·8 cm. transversely. The occipital horn and trigone of the right lateral ventricle was displaced forward and the trigone shifted to the left. The appearances were those of a right occipital tumour. The ventricular fluid contained 110 mg. of protein per cent.

Experiment.—On 2.12.48 after all air had been absorbed, two needle electrodes were introduced. On the right side the needle tip was 2 cm. behind, 1·1 cm. above the clinoid process and 1·7 cm. from the mid-line The needle's second electrode appeared to be in the lateral ventricle, and the other two were in the tumour substance. On the left side the needle tip was 2·8 cm. behind, 0·8 cm. above the clinoid process, and 1·1 cm.

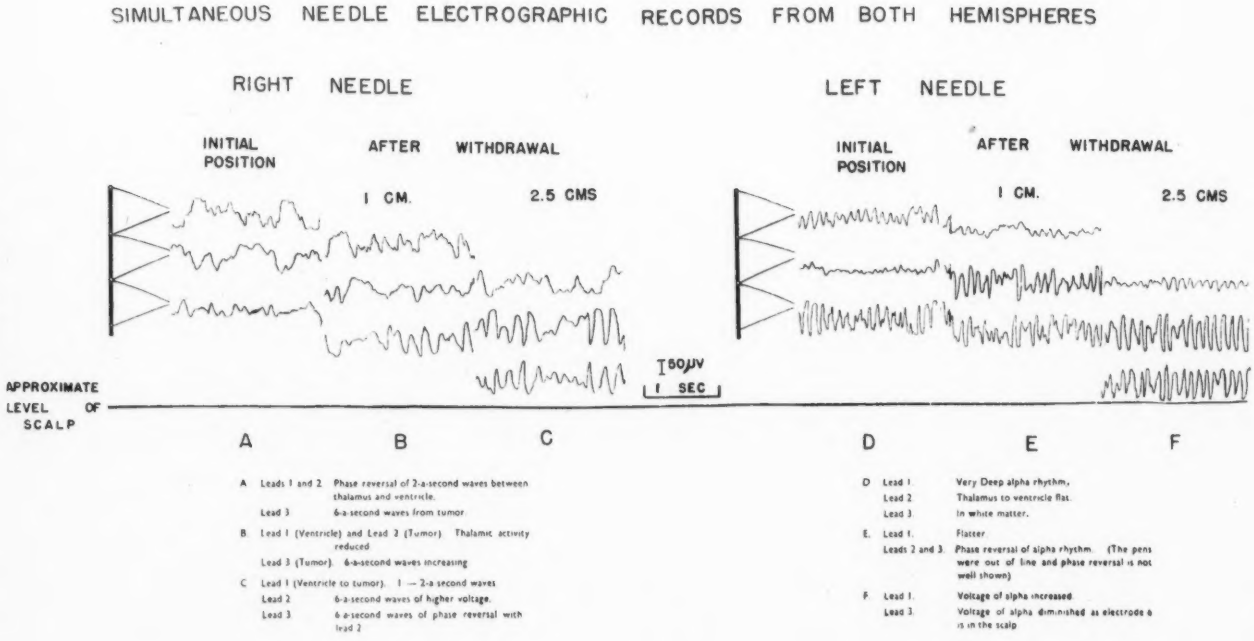

SIMULTANEOUS NEEDLE ELECTROGRAPHIC RECORDS FROM BOTH HEMISPHERES
RIGHT NEEDLE
LEFT NEEDLE
INITIAL POSITION
AFTER WITHDRAWAL
1 CM.
2.5 CMS
INITIAL POSITION
AFTER WITHDRAWAL
1 CM.
2.5 CMS
APPROXIMATE LEVEL OF SCALP
150μv
1 SEC
A
B
C
D
E
F
A Leads 1 and 2. Phase reversal of 2-a-second waves between thalamus and ventricle.
Lead 3 6-a-second waves from tumor.
B Lead 1 (Ventricle) and Lead 2 (Tumor). Thalamic activity reduced
Lead 3 (Tumor). 6-a-second waves increasing
C Lead 1 (Ventricle to tumor). 1 — 2-a second waves
Lead 2 6-a-second waves of higher voltage.
Lead 3 6-a-second waves of phase reversal with lead 2
D Lead 1. Very Deep alpha rhythm,
Lead 2 Thalamus to ventricle flat.
Lead 3. In white matter.
E. Lead 1. Flatter
Leads 2 and 3. Phase reversal of alpha rhythm. (The pens were out of line and phase reversal is not well shown)
F. Lead 1. Voltage of alpha increased
Lead 3. Voltage of alpha diminished as electrode is in the scalp

FIG. 2 (*See* legend p. 480)

from the mid-line. Its second electrode was on the edge of the thalamus, the third in the lateral ventricle and the fourth in the white matter (fig. 1). Simultaneous electrographic recordings were made from the right and left side and the results were compared. Both needles were withdrawn 1 cm. and further recordings were made; the needles were then withdrawn a further 1·5 cm. and the experiment repeated (figs. 1 and 2).

Right side: High voltage 2 a second waves occurred in the first and second leads with a phase reversal. More superficially and in the tumour tissue, low voltage 6 a second waves were seen (fig. 2A). When the needle was withdrawn 1 cm. the phase reversal which had been seen around the second electrode was less evident. The records from leads in the tumour were flatter, whilst those from the most superficial electrode showed an increase in voltage of the 6 a second waves (fig. 2B). When the needle had been withdrawn 2·5 cm. the tip was probably in the ventricle and medium voltage rhythmic 1–2 a second waves occurred. The superficial electrode must have left the tumour substance and a phase reversal of the 6 a second waves was recorded (fig. 2C).

Left side: Records from the terminal pair of electrodes showed a frequency of 9 a second, having all the characteristics of the cortical dominant frequency. When the needle was withdrawn 1 cm. the voltage of this rhythm dropped suggesting that it was being propagated, through the terminal electrode of the needle, from the cortex of the temporal lobe. Records from the middle pair of electrodes were relatively flat and simply showed irregular modulations of low voltage, mostly a reflection of the 9 a second alpha rhythms, while the superficial pair transmitted the alpha rhythm which was not seen on the right side. These records have already been described.

Although the patient's condition remained unchanged, she was not considered fit to undergo craniotomy and she was, therefore, sent home without accurate pathological verification having been completed.

Summary.—In this case a large right occipital tumour gave rise to 1 and 2 a second waves deep in the substance of the right hemisphere, with high voltage 6 a second waves arising in the cortex on that side. These 6 a second waves were confined to the cortex. The left hemisphere was normal, and showed an alpha rhythm of 9 a second in the temporal and parietal cortex, with no evidence of independent activity in the basal grey matter.

Case 2.—*Temporal tumour:* Hospital Case No. 95356. Male, aged 57. Admitted 17.11.47. Died 4.1.48. For two months the patient had had increasing difficulty with speech, for one month a gradual increase of left-sided headache. On examination he was drowsy, confused and disorientated and because he had a global dysphasia could not give his medical history. There was a marked right hemi-

plegia, the arm being most affected, without evident visual field defect. There was no papilloedema.

Electro-encephalogram (17.11.47) showed a severe left-sided abnormality mainly in the parietal region which consisted of high voltage rhythmic 5 a second waves with suppression of the dominant frequency of 9 a second (fig. 3A).

Ventriculogram (21.11.47): The brain needle was inserted through the left posterior parietal burr hole, and brain herniation occurred immediately from the dural wound, but the ventricular system was entered and 10 c.c. of C.S.F. were replaced by air. The lateral ventricles were moderately dilated. A filling defect was seen under the trigone of the left lateral ventricle. The septum pellucidum was deviated 1·5 cm. to the right of the mid-line by a deep temporal tumour which appeared to be invading the region of the thalamus.

He died on 4.1.48 and a post-mortem examination which was performed at another hospital confirmed that there was a tumour in the left temporal lobe.

Experiment (24.11.47).—There was still a small amount of air left in the ventricular system when the needle electrode was inserted through the left posterior burr hole. Its tip, which was in the tumour substance, was 3·5 cm. above and 3·5 cm. behind the posterior clinoid process and practically in the mid-line.

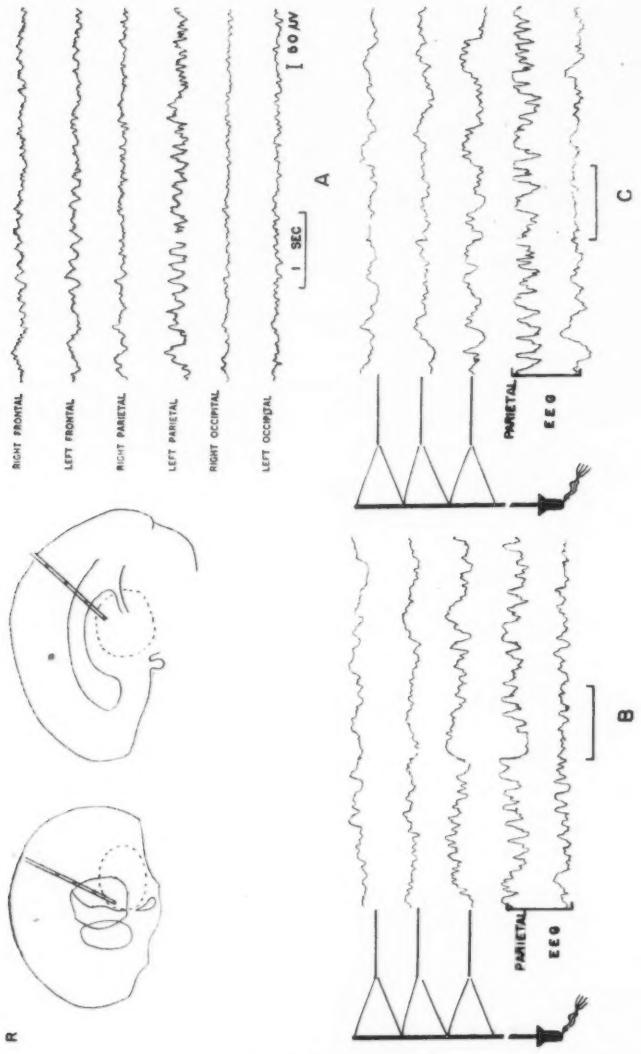
Samples of the records made are shown in fig. 3B and C. Records made from the scalp showed a 5 a second rhythm similar to those seen in the earlier E.E.G. with random 2 a second waves. Records from the needle tip and from the neighbourhood of the thalamus were relatively flat. No 5 a second rhythms were seen, but 2 a second waves of medium voltage were present.

Summary.—Records from a patient with a temporal astrocytoma showed 2 a second (delta) waves and 5 a second rhythms (theta) at the level of the cortex. Records from the thalamic region simply showed scattered 2 a second waves of lower voltage than those on the cortex. The faster waves were confined to the cortex.

Case 3.—*Parietal tumour:* Hospital Case No. 102338. Male, aged 65. Admitted 22.6.48. Died 2.8.49. A previously healthy man had had focal attacks spreading from the left hand to the arm for three months. They had become more frequent, more widespread and of longer duration as time progressed. Two months before admission he developed weakness and clumsiness of that hand, and two weeks later weakness and dragging of the left leg. He also had headaches accentuated by exertion. Just before admission he had become confused and drowsy. Six months previously he had had a troublesome dry cough and had lost weight.

The patient was drowsy and unable to co-operate, except in the most simple manner. He had a severe cough, was thin, and his general condition was poor. Except for basal moist sounds particularly well heard on the right side, the chest was normal. The optic discs did not show papilloedema, there was a left homonymous hemianopia which could not be accurately recorded, and also a left hemiplegia. Tendon-jerks were increased on the left side and there was an extensor plantar response. Tomography of the chest (22.6.48) suggested a bronchogenic carcinoma in the right upper lobe bronchus on the right side.

Electro-encephalogram (22.6.48) showed an unstable dominant frequency of 9 a second, the voltage of which was lower in the right posterior parietal region.



FIG, 3 (*see* legend p. 480).

Low voltage 4 a second waves were seen in the right temporal lobe with reduction in voltage of the normal frequencies posteriorly.

Ventriculogram (28.6.48): A cannula inserted through a right posterior parietal burr hole directed towards the glabella encountered a cystic cavity at a depth of 4 cm. 15 c.c. of turbid fluid were removed and replaced by air. Air was introduced into the ventricle through a left-sided burr hole. A specimen for biopsy was taken from the region of the cyst on the right side. The ventriculogram showed the

septum pellucidum displaced 1 cm. to the left. The body and trigone of the right lateral ventricle were displaced downwards and medially. There was an air-filled cyst in the parietal region (fig. 4). Microscopy of the specimen showed this to be a secondary carcinoma.

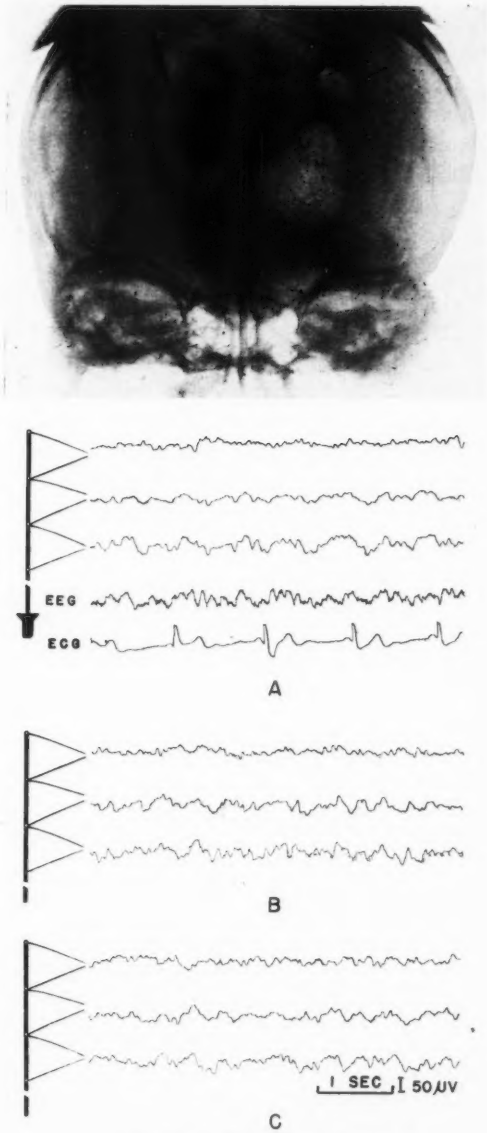


FIG. 4 (*see* legend p. 481).

Experiment (29.6.48).—The needle electrode was inserted through the right parietal burr hole, so that the tip was 4 cm. above and 2 cm. behind the posterior clinoid process. It was 2·2 cm. from the mid-line, and was in the lateral ventricle impinging on the superior surface of the thalamus. The second electrode was in the white matter, and the third and fourth electrodes were in the cystic part of the tumour. There was still some air in the cyst and in the ventricles, and the needle can be seen in position in the X-ray (fig. 4).

The needle electrographic record was abnormal. From the two superficial leads medium voltage 1–5 a second waves were seen to arise. They were in phase (fig. 4A). The thalamic record was flat but it was disturbed by a slow rhythm of low voltage which corresponded with the rate of the electrocardiogram. At times (fig. 4B) well-marked 4–5 a second waves were seen in the two superficial records when they were not recorded from the thalamus. In other parts of the record there was a relationship between potentials recorded from the deep and 2–4 cm. electrodes, and a phase reversal of some low voltage 4–5 a second waves was seen to occur (fig. 4C).

Summary.—A secondary carcinoma involving the right parietal cortex caused slow (delta) waves in the cortex, but the thalamic record was featureless except that slow waves arising at the deep extremity of the tumour were reflected in it.

Case 4.—*Frontal tumour:* Hospital Case No. 109447. Male, aged 56. Admitted 23.12.48. Died 20.1.49. A previously healthy normal man became apathetic and disinterested seven weeks before admission. His efficiency in his office deteriorated —he became irritable and truculent, and at home passive and untidy. His mental condition rapidly deteriorated, and a month later he became unable to look after himself—he was then incontinent and although alert, untroubled by it. Two weeks before admission he entered a mental hospital where the condition was recognized as one of organic dementia with severe intellectual impairment, retardation and poverty of initiative and movement. When first seen by us he was in a state of extreme hypokinesis—he occasionally answered questions in monosyllables but his mental state could not be assessed. No local disorders of function had been noticed.

Examination confirmed his mental condition. Early bilateral papilloedema was present. The pupils reacted sluggishly to light. Voluntary movement could not be tested due to inco-operation, but tone was increased especially on the right, there was poverty of voluntary movement, all movement being slow. There was also a coarse tremor on movement of any limb. Bilateral grasp reflexes and force grasping were present, the tendon-jerks were all very brisk, the abdominal reflexes present, and the plantar responses at first equivocal. All the abnormal signs were a little more marked on the left. A diagnosis was made of a large right frontal tumour infiltrating over the middle line and down towards the region of the third ventricle.

Electro-encephalogram (20.12.48) was abnormal. The dominant frequency of 8 a second was unstable and runs of 6 a second waves were seen in both parietal regions (fig. 5A). Medium voltage 4 a second waves were seen in the right frontal lobe,

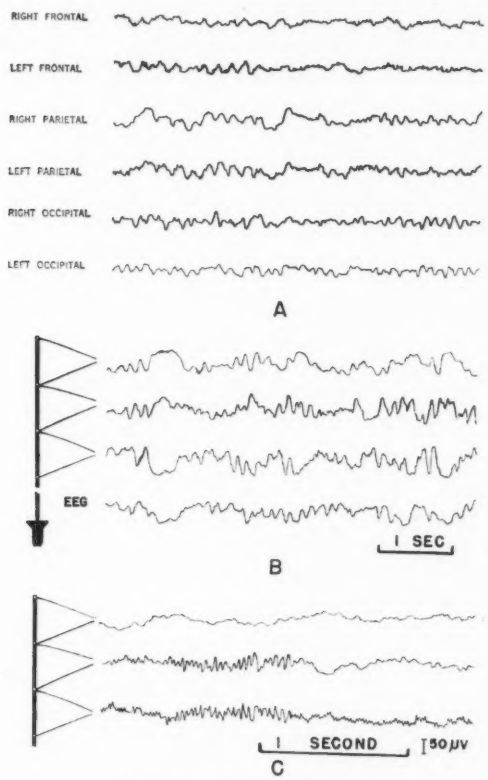


FIG. 5 (*see* legend p. 481).

and in view of the gravity of the clinical condition comment was made upon the relative absence of slower and more abnormal rhythms.

Ventriculogram (21.12.48): C.S.F. was found to be under greatly increased pressure. Both ventricles were encountered in normal position at a depth of 6 cm. Fair filling was obtained of the ventricular system. The septum pellucidum was shifted 3 mm. to the left. Both anterior horns were pressed backwards and the appearances suggested that there was a mid-line anterior tumour expanding into the right frontal lobe. The ventricular fluid contained 30 mg. of protein per cent but was otherwise normal.

Craniotomy performed by Mr. McKissock (29.12.48) exposed a malignant tumour involving the cortex of the right frontal lobe. In the centre of the superior frontal convolutions on the right side a purplish red area of tumour was seen to have all the appearances of a malignant glioma. A considerable quantity of this tumour tissue was sucked away to reduce pressure, but in view of its obvious malignancy and infiltration no attempt was made at further intervention.

Histological examination by Professor T. Crawford showed it to be a glioblastoma multiforme.

Experiment (23.12.48).—The needle electrodes were introduced

through a right posterior parietal burr hole, and the needle tip was 3·5 cm. behind, 6 cm. above the posterior clinoid process. It was 2·25 cm. from the mid-line. The most superficial electrode appeared to be in the scalp.

The needle electrographic record was abnormal. There was an unstable cortical dominant frequency of 8 a second, which appeared to be out of phase between the 2–4 cm. and 4–6 cm. records. Some runs of medium voltage 2 a second waves also occurred in these two records and were similarly out of phase; there was a spread of these slow bursts to the region of the thalamus (fig. 5B). Occasional short bursts of 22 a second waves were seen superficially which did not spread deeply.

Pentothal.—The effect of light anæsthesia by injection of 0·25 gramme of pentothal was to produce bursts of rhythmic 22 a second waves in the two superficial records whilst the thalamic record was relatively featureless (fig. 5C).

Summary.—A large malignant glioma of the frontal lobe gave rise to 2 a second waves in the E.E.G. These were reflected in the thalamic records, but no other spontaneous activity was seen except under light pentothal anæsthesia, when runs of 22 a second waves arose in, and were confined to, the cortex.

Case 5.—Thalamic tumour: Hospital Case No. 102361. Female, aged 16. Admitted 26.7.48. Died 19.8.48. Six months before admission there was an insidious onset of lassitude. On several occasions the patient had fallen asleep in the train on her way home, and so went past her station. She had had to change her job as a cashier because it seemed as if she was inefficient and unable to concentrate. Two months later she became forgetful of messages. On one occasion she went in search of an address and got lost; when she reached home she was dazed and slightly confused. Two months later she became most apathetic and on several occasions forgot how to dress; she just stood, did not know how to start, although later she was able to perform the appropriate action accurately.

During the month before admission she had night terrors, and had been found trembling and screaming, and often in a half-dreamy state—her mother saying that "She could not tell whether she was sleeping or waking."

In the two weeks before admission the patient's mental hebetude continued, and she had little attacks in which she shifted her gaze and jerked her head backwards. Sometimes when walking she would drop like a stone without warning, but was apparently not unconscious—these falls would occur once every two to three minutes for one or two hours, then she would become more drowsy and go to sleep. During this period she also had eight major epileptic convulsions, but except for slightly increased tendon reflexes on the left side there were no localizing physical signs.

On clinical examination her general physical condition was good. Although she was conscious she was almost inaccessible; she took no interest in her surroundings and was quite mute. She could not co-operate, except that she once held her hands up for a short while on request. The skull and cranial nerves were normal. Her optic discs were normal, and a threat reflex was present on both sides. In the arms posture was less well maintained on the left side. The reflexes were

sluggish and equal, and the abdominal reflexes were absent on the left side and sluggish on the right. The right knee-jerk was absent, the left present, but ankle-jerks were equal. The plantar responses were unobtainable. Sensation to pin-prick seemed normal throughout the body.

The patient was transferred for deep X-ray therapy (26.7.48) but died on 19.8.48, autopsy being refused.

Electro-encephalogram (29.6.48): The records were grossly abnormal. High voltage 1–2 a second waves seen constantly in all leads, were most marked on the right side where faster waves of 16 a second also arose. A phase reversal of the slow waves was recorded from the right side. The records were thought to indicate a deep parietal lesion which was worse on the right side (fig. 6A).

Ventriculogram (1.7.48) was performed through a right posterior parietal burr hole. The dura was not under tension; 8 c.c. of C.S.F. were removed and replaced by air. The septum pellucidum stood erect in the mid-line. The third ventricle was narrowed especially posteriorly which was reduced to a slit. There was elongation of the foramen of Munro and the upper part of the third ventricle did not fill at all. When the patient was prone the air remained in the anterior end of the third ventricle. It appeared that there was a mass around the ventricle, either a tumour of the wall or a bilateral thalamic tumour. This was supported on 20.7.48 when myodil which was injected into the right lateral ventricle could not be manipulated into the third ventricle, indicating that the foramen of Monro was obstructed.

Experiment (8.7.48).—The needle electrode was introduced through the right burr hole. The tip was 4·75 cm. above, and 3 cm. behind the posterior clinoid process. It was 1 cm. from the mid-line. The tip was on the edge of the tumour, the second electrode within the ventricle, and the other two electrodes were in the white matter. There was only a trace of air to be seen in the ventricles (fig. 6, diagram). The records were abnormal. There was an unstable superficial alpha rhythm of 14 a second, not seen in the thalamic record which was relatively flat. Sometimes medium voltage 2 a second waves were seen which appeared to arise between the tip—2 and 2–4 cm. electrodes, creating a phase reversal —these could also be recorded from the more superficial and scalp electrodes (fig. 6B). High voltage 3 a second waves were recorded with a phase reversal showing well between the deep pair of electrodes (fig. 6C), and high voltage deep solitary spikes were also seen (fig. 6D). The short burst of high voltage waves seen in fig. 6C was associated with some deep spikes, and in fig. 6E a burst of high voltage 16 a second waves was recorded only from the thalamus.

Summary.—A malignant tumour arising in the right thalamus, and probably affecting both, caused 2 and 3 a second waves to arise in the neighbourhood of the thalamus. Some of these waves were rhythmic, and they were reflected in the cortex. No 4–7 a second (theta) waves occurred. The thalamic tumour also caused a burst of spikes in the affected thalamus. Fast or slow waves of this kind were not seen in the thalamus with tumours elsewhere in the hemispheres, nor have they been found if the hemisphere is normal.

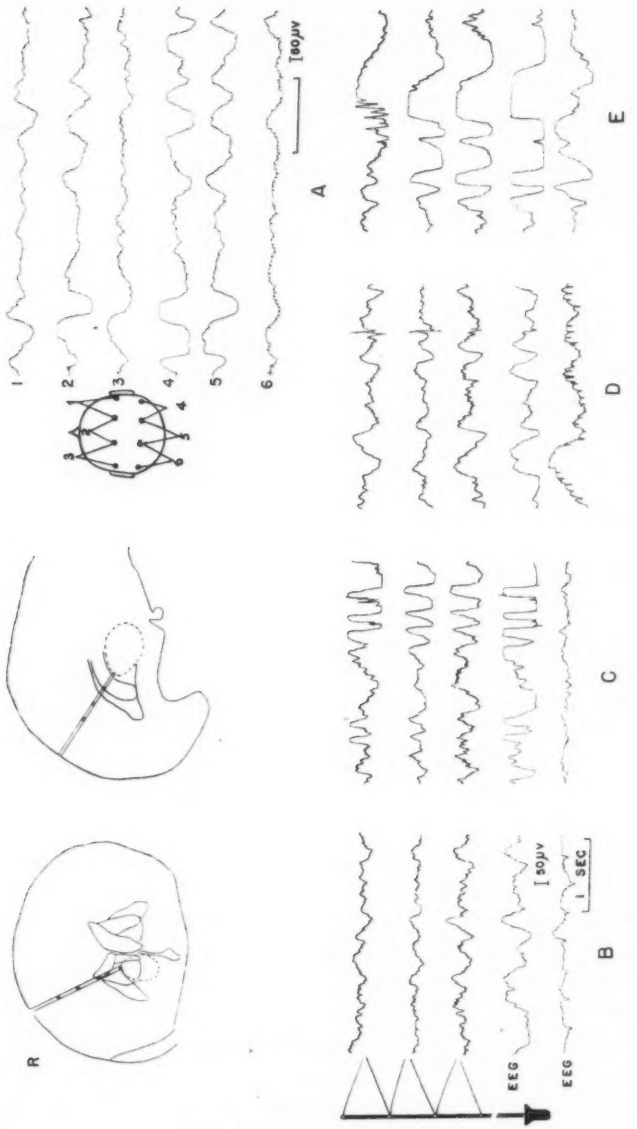


FIG. 6 (*see* legend p. 481).

CORTICAL ATROPHY

Case 6.—*Cortical atrophy.* Hospital Case No. 95680. Male, aged 58. Admitted 23.11.47. Although the patient was good tempered, alert and co-operative with normal speech, he did not know why he had been admitted to hospital and could

give no account of his previous medical history. He had no idea how long he had been in hospital, and could not tell the day or the date. His memory was grossly defective and he could not do any mathematical calculation. He had no physical complaints. His relatives gave a story of steady deterioration in intellect with limitation of initiative and interest for over three years. The central nervous system was normal except for a brisk jaw-jerk and brisk tendon-jerks. The plantar responses were flexor. There was moderate peripheral arteriosclerosis with a blood pressure of 140/100, but except for some emphysema there was no evidence of other physical disease.

X-ray chest (27.11.47); No abnormality detected.

Electro-encephalogram (27.11.47) was abnormal. The abnormality was generalized and the dominant frequency of 9 a second was disturbed in all leads by low voltage 6–7 a second waves. The records were quite symmetrical and no evidence of any local lesion was observed (fig. 7A).

Ventriculogram (8.12.47): A burr hole was made in the right post-parietal region. The brain was under normal tension. The ventricle was encountered at a depth of 5 cm. 70 c.c. of C.S.F. were replaced by air. The lateral ventricles were markedly dilated and measured 3·3 cm. from side to side. The third ventricle was not dilated and the fourth ventricle did not fill. There was considerable excess of subdural air and the appearances were those of cortical atrophy. The C.S.F. contained W.B.C. 5; protein 10 mg. per cent; globulin nil.

Experiment (8.12.47).—The needle electrode was inserted the same day through the right parietal burr hole. The tip was 2 cm. behind, 3·5 cm. above the posterior clinoid process, and 1 cm. from the mid-line (fig. 7, diagram). Although these outlines of the ventriculograms might suggest that the distal three electrodes are in the ventricles, the middle two are in fact in the thalamus, in its medial portion, where it forms the lateral wall of the body of the ventricle. A high voltage dominant frequency of 6–7 a second was seen in all three needle electrograms, but its voltage was greatest in the superficial lead. This rhythm was in phase and synchronous in all records. The rapid attenuation of voltage from the cortex inwards and the identity of the waves with those in the E.E.G. indicated their cortical origin and electronic spread. A rhythm of about 1 a second in the thalamic record was synchronous with the E.E.G. (fig. 7B). Runs of 16 a second waves lasting for not more than 0·5 second were seen in the thalamus. These did not spread to the cortex (fig. 7C).

Summary.—Generalized cerebral atrophy with presenile dementia was associated with rhythms of 6 a second in the E.E.G. No associated rhythms arose in the thalamus, but isolated runs of 16 a second waves of brief duration were confined to the thalamic region.

Epilepsy

Case 7.—*Idiopathic epilepsy.* Hospital Case No. 98014. Male, aged 21. Admitted 16.2.48. The patient had had three major epileptic fits during the previous month, and had had severe headaches. He said that the vision in his left eye had deteriorated. Witnesses described generalized convulsions without any focal onset. There was no personal or family history of convulsions.

On examination the outline of the left optic disc was less well defined than the

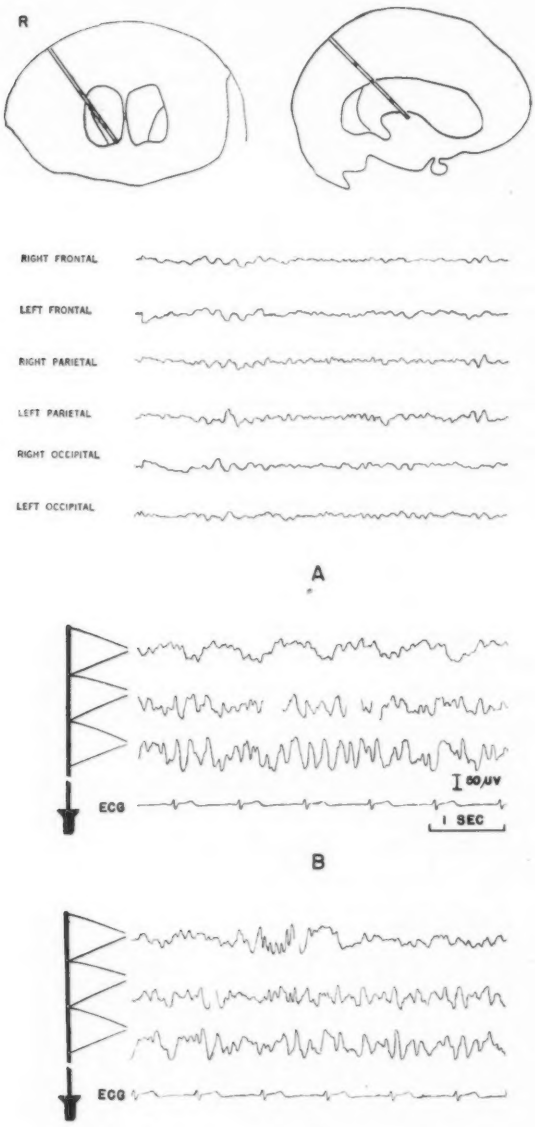


FIG. 7 (*see* legend p. 481).

right, and it was uncertain whether papillœdema was present. There were no abnormal signs in the rest of his nervous system.

Electro-encephalogram (3.2.48) was very abnormal. Rhythmic waves of 6 a

second were seen in both frontal regions, but they did not spread posteriorly. Episodes of high voltages 3 a second sine waves were seen in all leads simultaneously, and these were also most evident in the frontal region. These abnormal features represented epileptic discharges, but as the records from both hemispheres were identical throughout the time of recording, and as there was nothing to suggest any local abnormality, the changes were thought to be consistent with the diagnosis of idiopathic epilepsy (fig. 9A).

In view of the short history of convulsions, headaches, visual changes and the appearance of his fundi a ventriculogram was performed (12.2.48). The ventricles were perfectly symmetrical and no abnormality was detected. The C.S.F. was normal.

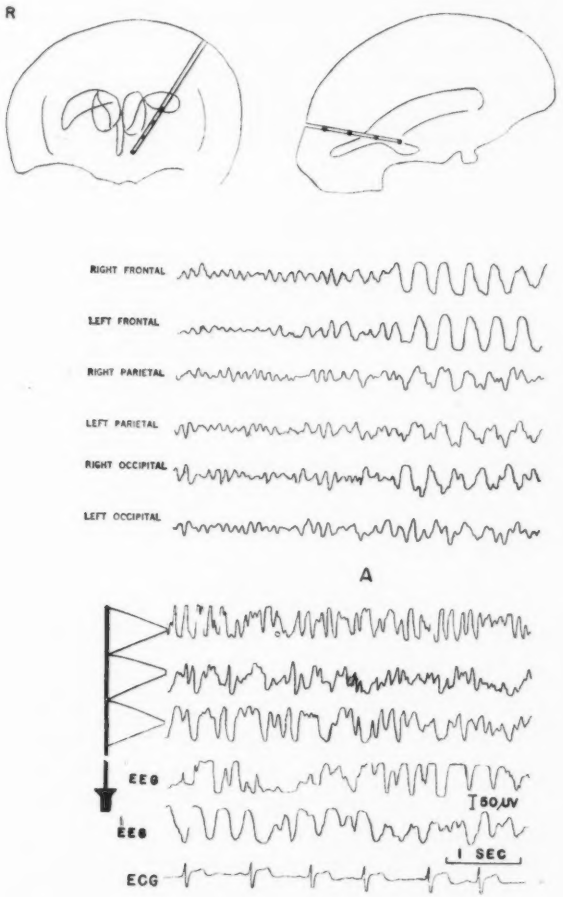


FIG. 8 (*see* legend p. 481).

Experiment (16.2.48).—The needle was inserted through a left parietal burr hole so that its tip was 2·5 cm. above and 3·5 cm. behind the posterior clinoid process, and 1 cm. from the mid-line (fig. 8, diagrams). The surface E.E.G. was similar to that recorded on 3.2.48 (fig. 8B). All the needle electrograms reflected the 8 a second rhythm. Phase reversals which were present, considered in relation to the position of the needle (*see* fig. 8) suggested that this alpha rhythm was being recorded both from the cortex over the convexity, and under the temporal lobe. There was no evidence that the basal ganglia contributed any independent rhythm. The rhythmic 3 a second "epileptic" rhythms were not associated with any changes in the thalamogram.

Summary.—In major epilepsy rhythmic 3 a second outbursts and an alpha rhythm of 8 a second were recorded from the temporal and parietal lobes. No independent rhythmic activity was recorded from the region of the thalamus.

Case 8.—*Symptomatic epilepsy.* Hospital Case No. 100666. Male, aged 46. Admitted 2.9.48. When admitted this man had epilepsy partialis continuans in the right face. He had a major convulsion in 1935, but was well until 1940 when he had had two more fits. In 1942 he had another fit and noticed numbness of the right side of his face and right hand with attacks of twitching in the affected areas. These symptoms were controlled by phenobarbitone. In April 1948 very frequent focal attacks with dysphasia recommenced and continued at intervals until his admission.

On examination the right side of his face was twitching and was weak. No other abnormal physical signs were found in the nervous system. The right arm was normal and the optic discs showed no swelling.

Electro-encephalogram (3.9.48) recorded during the attacks showed high voltage spikes arising in the left mid-parietal and mid-temporal regions (fig. 9A). Records from the right hemisphere showed a low voltage frequency of 9 a second. At times during the attacks some spikes were seen on this side also but at others the records were normal.

Ventriculogram (7.9.48) showed a large left mid-parietal filling defect. The third ventricle was tilted to the right, its roof being displaced 0·8 cm. The roof of the body of the left lateral ventricle showed a smooth depression and there was falx pressure in its posterior part.

Experiment (13.9.48).—The needle was introduced at a time when there was no air in the ventricle. The tip was 3·5 cm. behind and 2 cm. above the posterior clinoid process. It was approximately in the mid-line.

During a larval epileptic attack high voltage spikes occurred in the cortical records and in the electro-encephalogram, but they did not spread deeply. The thalamic records were featureless, and there appeared to be little or no spontaneous thalamic activity (fig. 9B).

Summary.—Focal symptomatic epileptic discharges, the result of a chronic parietal glioma, were confined to the cerebral cortex, and were not seen to be associated with any change in the part of the thalamus from which records were obtained.

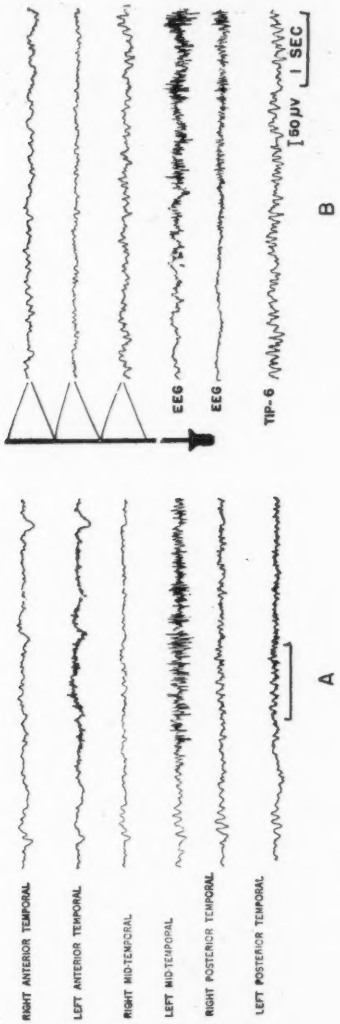


FIG. 9 (*see* legend p. 482).

Case 9.—Reflex epilepsy. Hospital Case No. 107412. Male, aged 26. Admitted 1.11.48. In October 1944 the patient sustained injuries to the right leg on active service, and ruptured the anterior tibial muscle. Four months later he felt a curious sensation in the injured part of the leg. The feeling increased, spread to the rest of his right side and he had a major epileptic fit. Attacks recurred which were not controlled by epanutin, phenobarbitone or bromides. Sometimes he had three major attacks a day. In all there was an aura beginning in the injured area, but he could sometimes abort them by gripping the leg. He noticed that knocking the

affected area might act as a trigger and his was considered to be a case of reflex epilepsy following peripheral injury.

There were no abnormal physical signs in the nervous system. There was a hernia of the tibialis anticus muscle and an epileptic fit could sometimes be provoked by sudden stimuli, such as tapping the area with a patella hammer.

Electro-encephalogram (3.11.48).—In the left temporal region episodes of 1 a second waves arose which were probably epileptic in nature. They were well localized and records from the areas were normal.

Ventriculogram (20.11.48).—The third ventricle and septum pellucidum stood erect and the lateral ventricle was normal in size, shape and position. There was air in the subarachnoid space, and the cerebral sulci were wider over the frontal lobes, suggesting a condition of cortical atrophy.

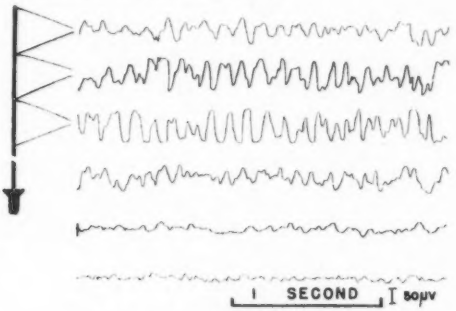


FIG. 10 (*see* legend p. 482).

Experiment (25.11.48).—The needle was inserted through the right parietal burr hole so that its tip was 3 cm. above, 5 cm. behind the posterior clinoid process, and 1½ cm. from the mid-line. There was only a small amount of air in the lateral ventricles.

The records showed an unstable cortical dominant rhythm of 9—10 a second with a high voltage. A constant phase reversal occurred between the two most superficial records (fig. 10).

The thalamic record showed a reflection of this rhythm, clearly conducted from the cortex, but was otherwise featureless. No epileptic discharges were recorded during the experiment even though the trigger zone in the right leg was stimulated.

Summary.—In a case in which focal epilepsy occurred in response to peripheral stimulation, the thalamic records contained no spontaneous activity independent of that arising in the cortex.

Case 10.—*Mixed epilepsy*. Hospital Case No. 96621. Female, aged 55. Admitted 18.12.47. The patients's medical history was uneventful until she had her first epileptic fit at 52. This was a minor attack, and another twelve attacks occurred during the next year. In July 1946 she had her first major fit in another hospital. During the next 17 months she continued to have episodes of major and minor epilepsy which were not controlled by phenobarbitone 3 grains and epanutin 3 grains daily.

She was alert, co-operative and intelligent, and her nervous system was normal. She had a diffuse nodular goitre. Her heart was clinically enlarged, the apex beat being in the fifth space 4 in. from the mid-sternal line. Blood pressure 170/90. Complete blood count was normal.

Electro-encephalogram (19.12.48) was normal. There was a low voltage dominant frequency of 11 a second on a series of steady base lines. No evidence of any epileptic activity was seen, and there was nothing to suggest any focal abnormality in the hemispheres.

Ventriculography (6.1.48): A brain cannula was inserted through a right posterior parietal burr hole. The pressure was normal and the ventricle was encountered at a depth of 5 cm.—20 c.c. of C.S.F. were replaced by air and the ventricular system was seen to be normal. The ventricular C.S.F. was normal.

Experiment (12.1.48).—Although the recording was carried out one week after ventriculography, there was still some air in the ventricles. The needle was inserted on the right side so that the tip was 2 cm. behind, 3 cm. above the posterior clinoid process, and 1 cm. from the mid-line.

The records were abnormal. Slow waves synchronous with the E.C.G. were recorded from the deep electrodes. Occasionally 2 a second rhythms were seen in the cortical record. These showed a phase reversal between the two superficial pairs of electrodes and were caused by the pulse. The thalamic records were usually flat and the unstable alpha rhythm of 10 a second did not reach it. Rapid pin-pricks to the left hand did not modify the rhythms appreciably. Pentothal 0·3 gramme was injected intravenously and 40 seconds later the superficial rhythms increased in rate to about 20 a second. These spikes were not seen in the thalamic record (fig. 11A).

At about the seventieth second high voltage 2–3 a second sine waves were seen generally, with a phase reversal between the superficial pairs of electrodes (fig. 11B); twenty seconds later these slow waves were well seen in the thalamic record (fig. 11C) another twenty seconds later the patient's jaw was noted to be moving, and at this time the record showed 18 a second rhythms occurring in the cortex and a minute later all slow wave forms had ceased and the records showed generalized 22 a second waves (fig. 11D). It seemed from these records that the slow coma waves were first seen superficially—this was confirmed by the phase reversal which suggested a cortical or sub-cortical origin. The thalamus showed these slow waves later. As the effect of the drug wore off the fast rhythms reappeared first in the superficial leads and later in the thalamic leads.

Summary.—In a late epileptic with major and minor attacks with a normal E.E.G. the thalamogram showed no spontaneous activity. During pentothal anæsthesia rapidly repeated spikes occurred in the cortex. These were replaced by 2 a second waves as anæsthesia deepened, to return with recovery. The different changes in cortical rhythms were reflected into

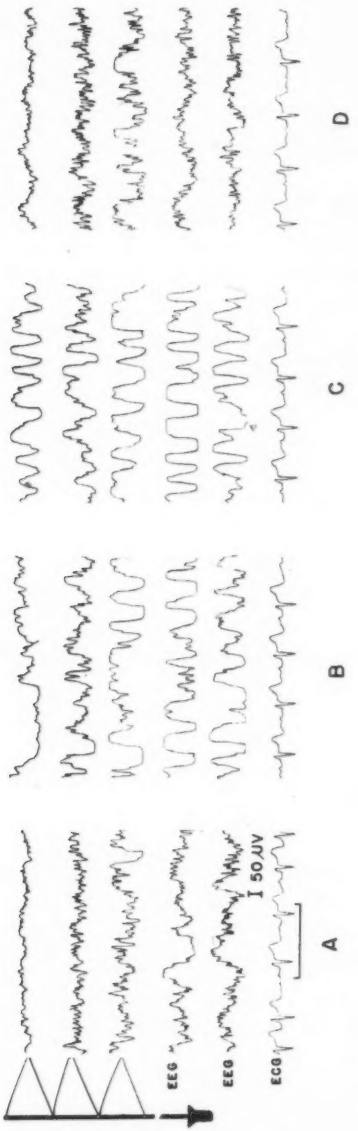


FIG. 11 (*see* legend p. 482).

thalamic records after an interval in each case. The slow rhythms were much more evident in the thalamus than were the fast spikes.

Case 11.—*Psychopath.* Hospital Case No. 96620. Male, aged 17. Admitted 17.12.47. This young man had been under the probation officer for about a year,

for stealing, and for trying to strangle a young boy. He had been very unhappy at home and had run away several times. He had been backward at school. He had had measles and pneumonia at nine months without convulsions. A year before his admission he had had an attack of dizziness when on a girder and fell 14 ft. He was unconscious for one hour. Six months later he began to have frequent attacks in which he would suddenly lose consciousness for a period of a few minutes, followed by confusion, headache, and occasionally weakness of the left side of his body. The day before admission he developed status epilepticus, and this had been stopped by intravenous pentothal in the National Hospital.

Electro-encephalogram (18.12.47) was abnormal. An alpha rhythm of 9 a second with a normal distribution was disturbed by 18 a second waves and by slow waves from 3–7 a second. No definite epileptic disturbances were seen.

Ventriculogram (19.12.48) was normal.

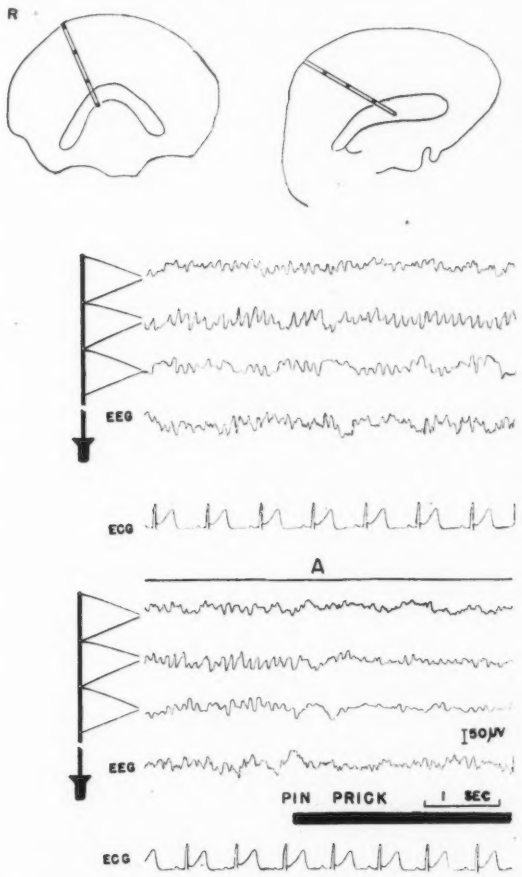


FIG. 12 (*see* legend p. 482).

Experiment (19.12.48).—The needle electrode was inserted after radiography whilst the air was still in the ventricles. The position of the electrode can be seen in (fig. 12, diagram). The tip of the needle was 3·5 cm. above, 1·5 cm. behind the posterior clinoid process, and 1 cm. from the mid-line. The records showed an unstable dominant frequency of 9 a second which had a lower voltage from the deep electrodes. There was a phase reversal of this rhythm between the two superficial pairs of electrodes (fig. 12A). At this time the technique of repeated recordings after serial withdrawal of the needle had not been devised. The thalamic record showed an intermittent irregular 2 a second rhythm which was not seen in the other records. Rapid pin-pricks to the patient's left hand caused suppression of the alpha rhythm, but the slow thalamic rhythm continued (fig. 12B).

Summary.—The electro-encephalogram of an epileptic psychopathic boy showed a generalized dysrhythmia consisting of a random mixture of fast and slow waves. An apparently independent slow rhythm was recorded from the thalamus. Inhibition of the alpha rhythm through pain did not affect the thalamic rhythm. There was no recognizable relationship between the thalamic and cortical rhythms.

Synthesis of Results

Examples of the spontaneous activity recorded simultaneously from the basal grey matter, the white matter, and the surface grey matter of the human cerebral hemispheres have already been given. These are representative of the findings in 21 cases, abnormal subjects, some of whom, however, had normal electro-encephalograms. Study of these examples show that the changes seen are diverse, but some general conclusions can be drawn. At this stage of an investigation which is not devoid of technical difficulties, and in which some of the limitations of the technique are evident, conclusions must be drawn with some caution.

The form of thalamic activity.—There seems to be no constant pattern of spontaneous rhythmic electrical activity in the human thalamus. The same is of course true of the cortex, but the dominant alpha rhythm is present in such a high proportion of normal subjects that the lack of any similar rhythm in the basal grey matter is striking. The needle electrodes were introduced blindly, without the aid of a stereotactic instrument, and their position was subsequently established with an accuracy of within 1 cm. in 3 dimensions by means of superimposing the X-rays of the needle in position and the ventriculograms. At least it was possible to establish the position of the electrodes in relation to such

structures as the thalamus, the caudate nucleus, the lateral ventricle, the third ventricle and the corpus striatum.

In the great majority of cases the terminal electrode was actually in or was in close relationship to the optic thalamus. In some instances it was in its inferior part, in others just deep to the ventricular ependyma sometimes in its medial, lateral, anterior or posterior parts. The whole of the thalamic area has been explored and it seems that no constant and characteristic rhythms arise from any part of it.

Thalamic inactivity.—As a rule, when evident spontaneous activity can be obtained from the scalp and directly from the cerebral cortex, the thalamic records are featureless and show no related spontaneous electrical activity. In such cases no demonstrable activity can be evoked by superficial stimulation. This absence of rhythmic activity appears to be absolute, for rhythms cannot be recorded even when the amplification is greatly increased. In particular there was no spontaneous rhythm comparable to the alpha rhythm; lesions of other parts of the hemispheres associated with slow rhythms were not reflected in thalamic slow activity; idiopathic and symptomatic *grand mal* was not associated with spontaneous thalamic activity when fits were not actually occurring; and a generalized cortical dysrhythmia was not associated with any spontaneous thalamic waves.

Spontaneous thalamic rhythms.—Although featureless records were usually encountered, spontaneous thalamic rhythms occurred, and were occasionally dramatic in their appearance.

Slow rhythms were seen in some cases. When they appeared they frequently ranged from 0·5 to 2·0 a second. They had a sinusoidal form, a rhythmic tendency and an amplitude of around 30 microvolts. They were not apparently related to the occurrence of cortical rhythms. They were found in relation to tumours deep in the hemispheres and involving the thalamus, and in association with an abnormal E.E.G. in an epileptic psychopath. Cortical slow waves which were recorded from the thalamus appeared to have been the result of direct and presumably electronic thread.

Fast rhythms.— Short-lived runs of sinusoidal waves having a frequency of 16 to 22 a second and a voltage of 20 to 30 microvolts were seen from time to time, in some cases interrupting an otherwise featureless thalamic record. These were seen in a case of tumour invading the thalamus (Case 5) and in organic dementia (Case 6). In contradistinction to the usual inactivity of the thalamus an example of episodes of spontaneous fast rhythms occurring in the thalamus in association with an abnormal state behaviour has been described by us (Williams and Parsons-Smith, 1949).

Induced thalamic activity.—No characteristic changes were seen in the thalamogram in states of impaired consciousness in response to painful stimulations, or with alterations in blood pH and of blood sugar, in spite of the appropriate changes in cortical rhythms.

Pulse artefacts.—In several cases rhythms made up of waves of irregular form having the same rate as the heart, but not being synchronous with it were recorded from the deeper electrodes. These very often showed a phase reversal at the ventricular surface of the thalamus. This finding was frequent and constant in its form, and greatly disturbed the records and our interpretation of them. The rhythms with this striking phase reversal were found to be present most frequently in patients who had only recently had a ventriculogram performed and who still had air in the ventricles at the time of recording, and we finally concluded that they were the result of alteration in the shape of the ventricles with each arterial thrust. The phase reversal arose at the electrode which was in the ventricular fluid, so that a rhythmic potential difference arose between that electrode and those in the deep grey matter and the overlying white matter. Presumably a movement occurs involving some slight distortion of the ventricle and compression of the indwelling air, the movement also causing a potential change.

Relation of thalamic to cortical rhythms.—It has been stated earlier that there is not as a rule an evident relationship between thalamic and cortical rhythms. The same frequency cannot be recorded in the two structures simultaneously, nor is there evidence of propagation of the rhythms, either from cortex to thalamus or vice versa, as judged from comparison of the time relations of waves recorded from different points along the needle and simultaneously from the cortex or scalp. Sometimes a wave of fairly high voltage can be recorded from all depths of the needle simultaneously, but in such cases we have concluded that the spread has been electronic. It is imperative to record from many points on the scalp at the same time as from the thalamus, lest local cortico-thalamic and thalamo-cortical relationships should be overlooked. The difficulty has been that even six channels of recording are inadequate for this purpose. Records have, however, been made at different times from frontal, parietal, parieto-occipital and temporal regions, sometimes from two positions in the same or on opposite sides of the head. In the few cases of organic brain disorder in which thalamic slow waves were seen in association with organic disorder of the brain, these waves were apparently independent of the spontaneous rhythmic electrical activity of the cortex.

Conclusions

These results, which are purely descriptive, do not require detailed comment. They seem to indicate that spontaneous rhythms such as occur in the cortex in normal and abnormal states do not usually arise in the thalamus. Damage to the thalamus by a tumour gives rise to slow waves as in the cortex. The two forms of rhythmic activity seen in thalamograms are: (1) A slow, interrupted, rhythm of ½ to 2 a second, seen with organic damage. (2) Episodes of 16 to 22 a second waves seen in a case in which the thalamus had been damaged, and in one in which there had been widespread cortical loss. The absence (in most cases) of any rhythms in the human thalamogram forms a base line for the study of thalamic discharges seen in other conditions.

Summary

(1) Simultaneous records have been made of the electrical activity of the cortex, subcortical white matter, and the basal grey matter, notably the optic thalamus. These records were accompanied by E.E.G.s, E.C.G.s and other observations. They were made with an electrode needle presenting four point electrodes each 2 cm. apart from its neighbour down the length of the needle. The metal tube of the needle was earthed and insulated, thereby acting as an electrical screen to the independent and isolated electrodes. The electrode needle was introduced with the usual technique for a ventricular puncture, and the positions of the electrodes were determined by ventricular radiology. The methods are fully described.

(2) Twenty-one subjects with diverse conditions, including organic brain damage and *grand mal* epilepsy, were studied. The encephalograms were modified in different ways during the periods of recording.

(3) In most circumstances the thalamogram is featureless, whatever is occurring in the electro-encephalogram.

(4) Slow rhythms (½–2 a second) occur when the thalamus is damaged by a tumour, and also occasionally when there is organic cortical damage.

(5) Episodes of fast rhythms (16–22 a second) arise in the thalamus in a small proportion of subjects.

(6) No relationship appears to exist between the spontaneous rhythms which may be seen in the thalamus in patients with organic brain damage, and the spontaneous rhythm of the cortex.

(7) No reflection of induced changes in cortical rhythms can be seen in the thalamogram.

(8) Although in some circumstances rhythms recorded from the cortex can be picked up from deeper structures there is usually a striking independence of thalamic and cortical activity.

(9) This preliminary survey suggests that with the methods so far available exploration of the electrical activity of the basal grey matter has no immediate application to the routine investigation of organic brain disorder. The results can however be used as a baseline for the experimental study of abnormal states of behaviour including epilepsy.

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LEGENDS OF DIAGRAMS

Fig. 1 (*Case* 1).—*Right occipital tumour.* Diagrams. Line tracings of antero-posterior and lateral ventriculograms, the approximate outline of the tumour being dotted. The shadows of the needles and electrode positions are shown.

A. *Electro-encephalogram.* In this and the succeeding electro-encephalograms, the amplification is equal in all channels and is indicated by a small vertical line representing 50 microvolts. Paper speed of 3 cm. a second is indicated in all instances by a horizontal line. Rhythmic 6 a second waves are seen in the right parieto-occipital region, which are not present on the left side (*see* text, Case 1).

B. Simultaneous right and left needle electrographic records. In this and succeeding examples of needle electrographic records, a representation of the needle appears on the left, the tip being uppermost and the thin lines directed towards the relevant tracing indicate the connexions of the input to the amplifiers. In this instance, the needle in the right hemisphere is represented above that in the left. Abnormal slow waves arise from the deeper pairs of electrodes on the right and there is a phase reversal between the records. The superficial record from the region of the tumour shows a rhythmic 6 a second wave similar to that seen in the electro-encephalogram (fig. 1A). Records from the left side are normal and similar to those seen in the electro-encephalogram.

C. Records from needle electrodes in comparable positions on two sides are shown. The number refer to the distance in centimetres of the electrodes from the needle tip. The actual records are similar to those described in fig. 1B.

Fig. 2 (*Case* 1).—This diagram illustrates records similar to those already described in fig. 1, and in the text. The records have been obtained when the needle electrodes in each hemisphere have been inserted at different depths. After the initial recording (A right and D left) the electrodes have been withdrawn 1 cm. (B right and E left) and then a further 1·5 cm. (C right and F left). Recording techniques are similar in each instance and identical with those in fig. 1.

Fig. 3. (*Case* 2).—Left temporal tumour. Diagrams. Line tracing of antero-posterior and lateral ventriculograms, the outline of the tumour being dotted and the shadow of the needle and electrodes outlined. The tip of the needle is in the tumour.

A. The electro-encephalogram shows 5 a second waves arising in the left parietal region.

B and C. Needle electrograms with standard technique. The 5 a second rhythms recorded in the electro-encephalogram are not seen in leads from the needle which are flat and show scattered 2 a second waves.

FIG. 4 (*Case* 3).—*Right parietal tumour.* Ventriculogram showing dilatation of the body of the left lateral ventricle with a large bubble of air within a cyst in the right parietal lobe. The needle traverses the tumour and its tip is in the thalamus.

A. Needle electrogram with one electro-encephalogram record from the overlying scalp. The electrocardiogram shows that the slow waves are not related to the pulse. The electro-encephalogram and the cortical records show slow rhythms which are not reflected in the relatively flat thalamic record.

B. and C. Needle electrograms showing relatively flat thalamic records. The slow waves in the more superficial records are shown in the text.

FIG. 5 (*Case* 4).—*Right frontal tumour.* A. The electro-encephalogram is abnormal. 6 a second waves occur in both parietal areas.

B. Phase reversal of the alpha rhythm and of the slower frequencies occur between the two more superficial records.

C. A rhythm of 22 a second is seen in the two superficial records across the cerebral cortex during light anæsthesia. These frequencies cannot be recorded from the thalamus. The paper speed is double that of fig. 5A and B.

FIG. 6 (*Case* 5).—Right thalamic tumour. Diagrams. Line tracings of the anteroposterior and lateral ventriculograms, the approximate outline of the tumour being dotted. The shadows of the needles and electrode positions are shown.

A. Electro-encephalogram from two transverse rows of electrodes. A phase reversal of the 1 a second waves occurs in the right posterior-parietal area.

B. Medium voltage 2 a second waves with a phase reversal between the two deeper records.

C. High voltage 3 a second waves arising deeply.

D. High voltage solitary spike arising deeply.

E. A burst of 16 a second waves arising in the thalamus.

FIG. 7 (*Case* 6).—*Cortical atrophy.* Diagrams. Line tracing of the anteroposterior and lateral ventriculograms with the needle in position in the right hemisphere. There is bilateral symmetrical ventricular dilatation due to widespread cortical atrophy.

A. Electro-encephalogram. The dominant frequency is disturbed by low voltage 6–7 a second waves in all leads.

B. Needle electrogram. High voltage 6 a second waves are confined to the superficial records. The thalamic rhythm is synchronous with the electrocardiogram (*see* text).

C. Burst of 16 a second waves arising in the thalamus which did not spread to the cortex.

FIG. 8 (*Case* 7).—*Idiopathic epilepsy.* Diagrams. Line tracing of the anteroposterior and lateral ventriculograms with the needle in position in the left hemisphere. The ventricles are normal.

A. Electro-encephalogram. Epileptic discharges of 3 a second sine waves arising in both frontal lobes.

B. Needle electrogram, with electro-encephalogram from the overlying scalp and a simultaneous electrocardiogram. An epileptic outburst arising in the cortex does not modify the thalamic activity.

FIG. 9 (*Case* 8).—*Symptomatic epilepsy.*

A. Electro-encephalogram. High voltage spikes are arising in left temporal region when movement began in the right hand in a focal epileptic fit. The records from the affected sides are unchanged.

B. Needle electrogram, with electro-encephalogram from the overlying scalp. The cortical spikes identical with those in A do not spread deeply and the thalamic lead is featureless.

FIG. 10 (*Case* 9).—*Reflex epilepsy.* Needle electrogram with electro-encephalogram from the overlying scalp. There is a phase reversal of the alpha rhythm between the superficial two records.

FIG. 11 (*Case* 10).—*Mixed epilepsy.* Needle electrogram, with electro-encephalogram from the overlying cortex. The effect of pentothal anæsthesia.

A. Light anæsthesia. There is an increase in the rate of the superficial rhythms.

B. Deeper anæsthesia. High voltage 3 a second sine waves have appeared. They show a phase reversal across the cortex.

C. Very deep anæsthesia. High voltage sine waves have spread to involve the thalamus.

D. Recovering. There is now generalized fast activity with disappearance of the rhythmic slow waves.

FIG. 12 (*Case* 11).—*Epileptic psychopath.* Diagrams. Line tracings of the anteroposterior and lateral ventriculograms, the approximate outline of the tumour being dotted. The shadows of the needles and electrode positions are shown. The ventricles are normal. Superimposed radiograms show that the needle tip was in the thalamus.

A. Needle electrogram. There is a phase reversal of the alpha rhythm across the cortex.

B. Suppression of the alpha rhythm is caused by pricking the patient's left hand. The thalamic record is unchanged.

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Notices of Recent Publications

The Sherrington Lectures. I. Sensory Integration. By E. D. Adrian. Published by the University Press of Liverpool. Pp. 20. Price 1s.

The Council of the University of Liverpool was fortunate in finding in the person of Professor Adrian one so obviously fitted to inaugurate the series of Sherringtonian Lectures founded in that University. The Contribution made by Adrian and his collaborators to our understanding of the afferent mechanisms of the nervous system compares worthily with that made by Sherrington in respect of the corresponding effector mechanisms. In his lecture now published by the University he claims that tribute is due to Sherrington not only for his additions to our knowledge of the individual spinal reflexes but also for having "made us look at new things in a new way," and for having "fit a new part of the puzzle together so that we begin to see a little more of the general design." But in the embarrassingly prolific work of others which has appeared since his publication in 1906 of "The Integrative Action of the Nervous System," the emphasis is all on the analysis of the more elementary spinal reactions and there has been little corresponding advance in the analysis of integrated behaviour.

The individual spinal reflex arc is an artefact of experimental technique: Sherrington's demonstration of the terms of interaction of such reflexes forms the basis of studies on the postural activities shown by the thalamic animal of Magnus and Rademaker. These are still concerned largely with physiological abstractions—and further work on the effector mechanisms of the cerebral cortex reveals to the full the increasing difficulties of this problem of integration in relation to the intact nervous system. Adrian traces the development of reflex neurophysiology to this stage and having left these investigators to stand patiently exploring some entrance to the complexities of cortical integration from the effector side, he turns to consider the progress made towards the same goal from its opposite side, along the path from the peripheral sensory receptors up to the cortical registration areas.

Perhaps the most impressive part of his lecture is that which traces the clear parallels which exist between results achieved in the sensory and in the motor fields. Sensory receptors like spinal reflexes may be analysed in isolation but never work in isolation. All sensory receptors show in response to stimulation a focus of maximal activity surrounded by a zone of centrifugally diminishing activity. Sherrington's demonstration of the excitatory and inhibitory fringes of motor activity, the subliminal fringes of motor activity, was the essential basis of all nervous integration at every level on the motor side. Adrian has demonstrated the existence of similar subliminal fringes of sensory activity at all corresponding levels: they are as evident in the sensory cerebral cortex as in the peripheral receptor mechanisms. He here sets forth the evidence for their existence in respect of such diverse sensations as Touch, Vision, Hearing and Smell, Peripheral stimulation, however refined and selective, never results in stimulation of single peripheral receptors and never gives rise to precise and limited activity in the cortex; it provides "afferent maps" of activity the recognition of which depends upon the identification of their patterns as a whole: "the surface of the brain may be said to have a small scale map of what is happening at the surface of the body—a map expressed by the density of the impulse discharges reaching the different parts of the receiving areas," in this respect "the three large sense organs of the head are built on a common plan," a plan which Adrian has elsewhere shown to be involved in the recognition of touch when this is perceived in its precise special setting.

At this point in his address Adrian finds himself in the same position in relation to cortical integration as that in which he earlier left the reflex neurophysiologists, looking for a way into the mysteries of those organized responses which underlie behaviour. He reminds us that one of the normal results of sensory recognition is motor exploration: the child explores with his hands the object which he sees; the pig does the same with its snout. In these ways tactual and visual patterns of the cortex are integrated into percepts which are projected back into the environment. In many common experiences of life it is obvious that our perceptions are enhanced by the integration of such sensory patterns; the enjoyment of food by the simultaneous sensations from smell, taste and motor activity in our tongue and gullet; the spectacle of performed music or of ballet by the temporal overlapping of sensations from the eye and from the ear. Between

those cortical patterns of sensation and its effector mechanisms of exploration lies the domain of thoughts and ideas: in essence, the mind: "beyond the receiving areas in fact the physiologist loses all sight of these maps of the outer world which the sense organs are sending in. Ultimately there will be appropriate physical action, speech or other skilled movement, directed by the nerve cells in the motor area of the brain, but between the sensory and motor actions there is the whole process of abstraction and integration and the whole of the vast territory of the association areas in which to look for the signs of it."

Of these areas Adrian considers that the two fundamental properties are those of memorizing and of abstracting or detecting general relations. Of these two properties it may be doubted if memorizing, without further qualifications, is entitled to such prominence. For when we say that in the spatial dispositions of certain lines we recognize the letter "A" we are making an abstraction which is as fundamental, as complex and as remote from expression in terms of neuronic activity as is involved in our recognition of a familiar landscape or of a remembered voice. On the other hand when we say that we remember, we may refer only to our ability to respond predictably and recurrently to sensory patterns which we have previously experienced. This we could do without any relation to their "significance": in which case it would involve no more than the exhibition of any other reflex activity at any level of nervous organization. But if by memory we mean our ability to recognize certain sensory patterns when they are represented or to evoke at will the images or thoughts corresponding with these significant sensory perceptions, then the only noteworthy process to which we are referring is the other process of mental activity, i.e. that which endows these patterns with significance, the power of "abstracting from the sensory data just those particular features which have become significant."

Adrian suggests also that the search for the mechanism of "this essential feature of cerebral activity" can be narrowed down to the neighbourhood of the particular receiving area involved in a given case, because Lashley has shown that it can survive widespread destruction of parts of the brain remote from this area and because with our eyes closed we can think without any detectable disturbance in the electroencephalogram. From these observations he suggests that "the process of abstraction, detecting significant relations in a pattern of nervous activity, can be carried out without involving very much of the sheet of nerve cells," and "whatever is happening when we think is therefore not enough to modify the activity of much of the cortex." This is a conclusion which is hard to accept in terms of understanding personality and behaviour; it may be that the thumb and finger of the electro-encephalograph is in its present form too coarse to plumb these activities to which he has referred as "mental."

He expresses his belief that such speculations upon the integration processes of the brain cannot do more than pass the time until we know more about less complex adjustments, and that we shall do well to seek first for more information about these, "to study the integration of sensory patterns which are not so full of meaning and do not involve the mysterious association between brain and mind. In fact Sherrington's method is still the most likely to succeed: the method which studies nervous activity in rigidly defined and simplified conditions with the express object of learning what will happen when the conditions are more complex." In an age when enquiry into the the mainsprings of emotion and behaviour is so often obscured by appeals on behalf of mental reactions which are ill-defined because not rigidly conceived by their authors and when medical psychologists are prone to borrow a semblance of authority by the reckless use of the terms of neurophysiology, this belief cannot be over-valued and by his deliberate avoidance of such speculations Adrian bears witness to that patience and continence in the face of difficulties which is the supreme test of the scientific method.

E. A. B. P.

Clinical Examination of the Nervous System. By O. H. Monrad Krohn. Ninth Edition. 1949. London: H. K. Lewis. Price 16s. 6d.

This edition has the qualities, good and less good, noted in reviews of earlier editions. It is in effect a hybrid, seeking to combine the characteristics of a textbook of neurology and those of a technical manual of examination methods. As the former it is necessarily inadequate, while as the latter it is unbalanced and swamped by matter not relevant to its title, reflecting also the tastes of the author rather than providing a complete methodology. Its bibliography remains almost exclusively Scandinavian, comprising papers by the author or those who are named as his former assistants. Modern neurology is surely more catholic than the author supposes and has many points of active growth. These are defects in a work presented to the English-speaking neurological world. Their remedying and a ruthless pruning of the book would add immeasurably to its value, for it contains much of great usefulness.

Sex Variants, a Study of Homosexual Patterns. By GEORGE W. HENRY. 1948. Pp. xxiv, 1128. New York: Paul B. Hoeber. London: Hamish Hamilton. Price 40s.

This large volume is published as a source of material from which the reader may draw his own conclusions. It includes detailed accounts of the life-histories of forty homosexual men and forty homosexual women. In fact, a challenge is offered to the reader to make what he can of the material provided, a challenge that few are likely to take up. It would perhaps have been more encouraging if the author himself had made some attempt to draw conclusions from his researches; but he has refrained from this and contents himself with a few pages of desultory and largely unconnected comments entitled "Impressions", which are mainly concerned with the social and legal aspects of homosexuality. Most readers would have liked to have used such a source book as a means of checking their favourite theories, psycho-analytical, endocrinological, genetical or constitutional. Whatever their field of primary interest, however, they are likely to complain that the material provided is insufficient. It is to be feared that, in view of the colourful human interest of the stories, the commonest purpose the volume will serve will be that of a bedside book in the guest-room.

The genetical basis of homosexuality is a subject of considerable interest, and it is one of the merits of this case collection that the family records are given in great detail. If we do a little of the work which the author might as well have done for us, we can draw some interesting observations from the family histories. First, there is no indication of the shift in the sex ratio in the sibs, which was postulated on theoretical grounds by Lang and also found by him. According to Lang's hypothesis there should be an excess of males among the sibs of male homosexuals, of females among the sibs of female homosexuals. In this material there is an excess of females among the sibs of the males, of males among the sibs of the females. Some authors have associated homosexuality with a general tendency to psychopathy, neurosis and psychosis among the relatives of homosexuals. Among the 160 parents in the present material there were 36 cases of neurosis, psychosis, psychopathy or suicide, which does not seem very excessive, and in the sibs the proportion of the psychiatrically abnormal is approximately half as much. On the other hand the frequency of homosexuality in these families does seem to be raised. Two mothers and 18 sibs were practising homosexuals, and there were further cases among aunts, uncles, cousins, etc. A curious point is shown in that 21 of these secondary cases of homosexuality were related to the propositus through the mother, while only 7 were related through the father. In addition, as the author himself observes, both with the male and the female homosexuals there is a general tendency to a reversal of the normal relationship between the parents, in that the mothers tended to be the more aggressive, the fathers more submissive. This reversal seems to be more marked and more constant in the parents of the strictly homosexual cases than in the parents of the bisexual subjects.

One receives the impression that this material might well have repaid a careful and systematic analysis and the use of statistical methods, as a check on some current theories of causation.